Human cardiovascular baroreceptor function and blood pressure control : effects of aerobic fitness and microgravity

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HUMAN CARDIOVASCULAR BARORECEPTOR FUNCTION AND BLOOD PRESSURE CONTROL – EFFECTS OF AEROBIC FITNESS AND MICROGRAVITY

By

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BY FAILING TO PREPARE...
WE PREPARE TO FAIL! *Wellington*

ABSTRACT

INTRODUCTION. Orthostatic intolerance has been reported in endurance athletes and astronauts returning from orbit. The exact nature of the cause in each instance has yet to be determined, however, an alteration in baroreceptor function is one potential mechanism. This study measured the baroreflex function of subjects in exercise trained and detrained states at +1G and during microgravity. METHOD. Seven athletic subjects had their aerobic fitness, blood volume, tolerance of lower body negative pressure (LBNP) and carotid and cardiopulmonary baroreflex sensitivity measured before and after a period of exercise training or detraining. Seven untrained subjects had similar measures taken before and after a control period. The cardiovascular response to Valsalva's manoeuvre (integrated baroreflex response) of the test subjects was also measured at +1G (supine and 6° head-down tilt) and during microgravity (parabolic flight), in both states of fitness. RESULTS. Detraining lead to significant reductions ($p < 0.05$) in aerobic fitness (maximum oxygen uptake from 63.5 ± 9.9 to 53.6 ± 5.9 $ml.kg^{-1}min^{-1}$), blood volume (from 5.7 ± 1.0 to 5.3 ± 0.9 l) and carotid baroreflex gain (from 5.44 ± 3.37 to 2.46 ± 1.02 $ms.mmHg^{-1}$) and a significant increase ($p < 0.05$) in tolerance to LBNP (from 785.7 ± 206.7 to 966.1 ± 337.9 mmHg.min). No change in cardiopulmonary baroreflex gain was found. Integrated baroreflex gain during microgravity was not affected by trained state (trained 13.2 ± 7.2 $ms.mmHg^{-1}$, detrained 14.1 ± 6.6 $ms.mmHg^{-1}$). The gains measured during microgravity for both fitness states were, however, significantly less than ($p < 0.05$) those measured during head-down tilt (trained 25.9 ± 10.3 $ms.mmHg^{-1}$, detrained 23.1 ± 5.8 $ms.mmHg^{-1}$) and when seated (trained 24.8 ± 13.1 $ms.mmHg^{-1}$, detrained 22.9 ± 6.6 $ms.mmHg^{-1}$) at +1G. CONCLUSIONS. A reduction in endurance fitness can increase tolerance to LBNP. The lack of change of the integrated and cardiopulmonary baroreflex and reduction of carotid baroreflex gains with change in endurance fitness indicates that the improved tolerance was not directly associated with baroreflex sensitivity. Integrated baroreflex sensitivity is, however, affected by acute exposure to microgravity possibly as a result of changes in thoracic cavity pressures and cardiac filling characteristics resulting from the loss of gravity.

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In conclusion I would like to dedicate this work to the lights of my life, Lisa and Kiran Scott.

ABBREVIATIONS AND UNITS

ABBREVIATIONS

AVP	= Arginine Vasopressine
BRSI	= Baroreceptor Sensitivity Index
F_ACO	= Fractional concentration of carbon monoxide in the alveoli
F_AO_2	= Fractional concentration of oxygen in the alveoli
F_EO_2	= Fractional concentration of expired oxygen.
F_ECO_2	= Fractional concentration of expired carbon dioxide.
Fig	= Figure
F_IO_2	= Fractional concentration of inspired oxygen (assumed 0.2096).
F_IN_2	= Fractional concentration of inspired nitrogen (assumed 0.7904).
LBNP	= Lower Body Negative Pressure
M	= Haldane's affinity ratio (Appendix G)
P_B	= Ambient barometric pressure (mmHg).
P_{H2O}	= Partial pressure of water, saturated at ambient temperature (mmHg).
PRA	= Plasma Renin Activity
t_r	= Room temperature (°C).
V_E	= Volume of expired air per minute (litres).
$\dot{V}O_2max$	= Maximum Oxygen Uptake
[HbCO]	= concentration of carboxyhaemoglobin
$[HbO_2]$	= concentration of oxyhaemoglobin
$[F_{ET}CO_2]$	= fractional end tidal carbon dioxide concentration

UNITS

d	= day
hr	= hour
l	= litre
min	= minute
mmHg	= millimetre of mercury
ms	= millisecond
s	= second
wk	= week

ADDENDUM

ALTERATIONS

Page, Para, Line	Reads:	Should read:
16,2,4	Crampton	Ward-Crampton
16,2,5	Ward; Ward et al	Ward et al
20,1,6	carotid nerve	carotid sinus nerve
22,3,6	angiotensine	angiotensin
26,2,5	stimulated	unloaded
33,2,4	receptor	baroreceptor
47,2,2	rennin	renin
52,2,3	5°C	5°
57,1,5	principles	principal
58,3,5	affected	effected
83,Fig 3.13	subjects	subject
113 Table 4.4,7	Baseline	Pre-syncope
114,1,1	4.7	4.5
120,1,5	initial	final
120,1,5	final	initial
123,1,5	than the	than day 3 of the
124,2,2	mean BRSI	mean responses to Valsalva's
124,2,10	+29.7	+30.3
156,3,8	receptors	vessel wall
160,2,3	Slight	Sleight
179,1,8	posses	possess

ADDITIONAL ABBREVIATIONS

1G	= 1 x Earth's Gravity
bpm	= beats per minute
HDT	= Head Down Tilt
Gx	= Acceleration along the fore/aft axis

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1.0 INTRODUCTION

The writing of this thesis coincides with the dawn of a new century and indeed a new millennium. One hundred years ago mankind was essentially an earth bound race; we could speed across the ground and ocean, we could communicate from afar and even float through the air, but we were unable to transport ourselves through the sky anything like as efficiently as we could on the surface of the earth. In the space of a single lifetime we have moved from that state to one in which interplanetary travel is possible and the promise of interstellar travel, although not imminent, is theoretically conceivable. The rate of human progression in the last 97 years since the Wright brothers flew Kitty Hawk into the annals of history has been staggering. This pace of technological advancement if continued through the next century (and the indications are that it will in fact be exceeded!) is such that my grandchildren will be able to experience the wonder and pleasure of traveling through space in much the same way as we now perceive air-travel.

Commercial orbital and sub-orbital flights will come in to being in the near future. The United State's National Aeronautics and Space Administration (NASA), the European Space Agency (ESA) and independent organisations such as Rotary Rocket Inc have devoted a great deal of time and money into the research and development of sub-orbital/orbital spacecraft. The next 10 to 20 years leading up to commercial space flight will see a huge increase in manned space travel (Fawkes, 2000). This will occur as a result of the building of the International Space Station, the next generation of re-usable spacecraft, space tourism and quite possibly the first manned mission to Mars. The International Space Station will be functional by 2010, but will necessitate an increase in human activity in space

FIGURE 1.1. ROTON. A vertical takeoff, single stage to orbit design which will descend by rotors. Currently being manufactured in Redwood, California.

for its construction. The smaller orbital craft although in the research and development stages at present, will enable small groups of people to enter space for research, industrial purposes and exploration. At present there are over 13 independent commercial spacecraft projects indicating the possibility that commercial space travel will grow and eventually outstrip Government funded enterprises.

We cannot escape the inexorable movement of mankind in to space. We must, therefore, have a detailed understanding of what happens to humans during and after exposure to the weightless (microgravity) environment. Just as the aviation medicine pioneers of the last 75 years identified and overcame the problems associated with high altitude, high speed flying, so it is that we must examine the effects of the most demanding of environments, space. By conquering or circumventing the problems posed by space travel, we may continue to expand our horizons and progress through the next millennium as effectively as our predecessors did the last.

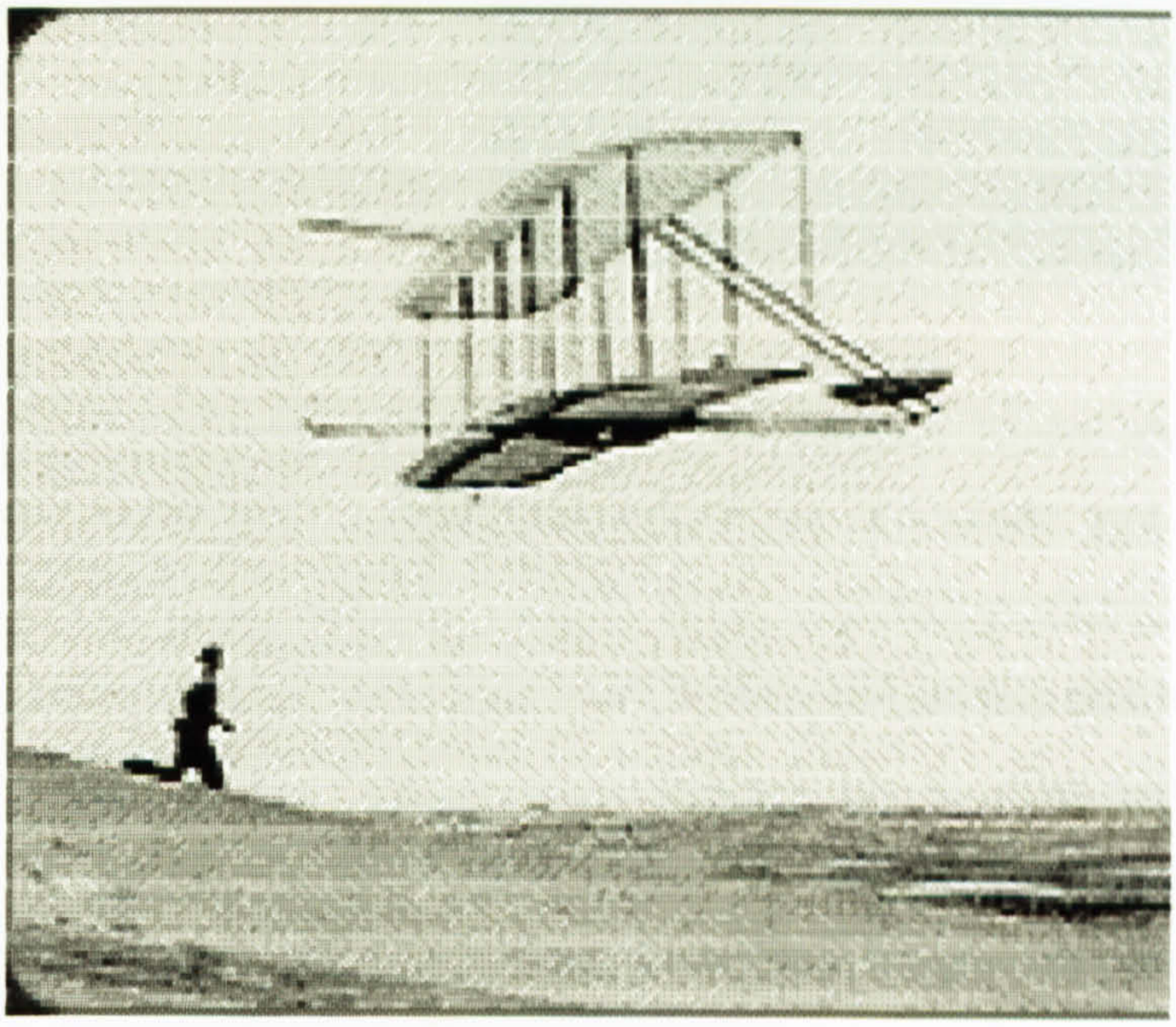

FIGURE 1.2 THE WRIGHT BROTHERS TEST FLYING KITTY HAWKE

1.1 BACKGROUND

There is evidence to suggest that high levels of endurance training in humans may lead to poor blood pressure control i.e. the failure to produce adequate cardiovascular responses when exposed to gravitational challenges such as standing or head-up tilt (Stegemann et al., 1974; Stevens et al., 1992; Geelan and Greenleaf, 1993; Raven and Pawelczyk, 1993; Savard and Stonehouse, 1995). Observations from space missions and ground-based simulations of microgravity indicate that astronauts also have a reduced tolerance to gravitational stress after space flight (Berry, 1969; Vorobyov et al., 1983; Buckey et al., 1996b). It is still unclear as to exactly which elements of the blood pressure control system are involved, but differences in baroreflex sensitivity between fitness states (Mack et al., 1987; Smith et al., 1988a; Evetts and Russomano, 1995) and between the pre- and post-mission states of astronauts (Fritsch et al., 1992; Fritsch-Yelle et al., 1994) have been observed.

FIGURE 1.3. SOVIET COSMONAUT SUFFERING FROM POST MISSION ORTHOSTATIC INTOLERANCE

Certain other factors may have an impact on blood pressure control after exercise training and/or microgravity exposure, examples of which are the mode and degree of training (Lightfoot et al., 1994; Savard and Stonehouse, 1995), somatotype (Klein et al., 1980), blood volume (DiCarlo and Bishop, 1990; Mack et al., 1993) and genetic endowment (Convertino, 1987). Although many previous studies have examined one or more aspects of this area of interest, it is becoming increasingly apparent that the relationships between blood pressure control and fitness and exposure to microgravity are not simple, may not be linear (Levine, 1993) and may be made unclear by the plethora of techniques and conditions used to study the interactions (Shvartz and Meyerstein, 1972; Charles and Richardson, 1981; Barney et al., 1988; Blamick et al., 1988; Pawelczyk and Raven, 1989; Fortney et al., 1992; Buckey et al., 1996b).

The results of previous work have not resolved the question as to whether fitness per se or an inherent predisposition to be able to become fit, leads to inadequate cardiovascular responses to standing i.e. orthostatic intolerance. Observations suggest that the increased plasma volume derived from exercise training (training induced hypervolaemia) may play an important role in the aetiology of orthostatic intolerance (Mack et al., 1993). It is possible that orthostatic tolerance is affected only in individuals who are sufficiently fit to have training induced hypervolaemia and then only in those who have had this condition for a significant length of time (Raven, 1993). Is it possible, therefore, for an astronaut who has improved his/her endurance fitness over a number of years prior to a mission, to be open to a cumulative adverse effect of fitness and microgravity exposure upon blood pressure control? If this is the case is there presently the possibility of a very fit shuttle pilot fainting when reacting to unexpected acceleration forces during shuttle re-entry? In a few years from now will fit people (athletes, fitness professionals, dancers etc) need special guidance and countermeasures during and after orbital flight?

2.0 REVIEW OF LITERATURE

2.1. ORTHOSTATIC TOLERANCE AND FITNESS – THE PROBLEM

One of the most contentious issues in sports science and space physiology is whether a relationship (causal or indirect) exists between orthostatic tolerance and endurance fitness. The difficulty in solving this problem derives from a number of factors. The first is that the relative terms and concepts do not appear to have consistent/recognised definitions. Confusion arises primarily from the increasingly common use of operational definitions[1] of orthostatic tolerance as opposed to a linguistic definition. Webster's unabridged dictionary (Steinmetz, 1997) defines 'orthostatic' as "*...relating to or caused by the erect posture...*" The word 'tolerate' is given a medical definition of "*...to endure or resist the action of...*" Consequently, the correct definition of 'orthostatic tolerance' might be '*the ability to resist the effects related to or caused by the erect posture*'.

The primary physiological effects of standing can be reproduced by other means, principally head-up tilt and lower body negative pressure (LBNP). For decades these means have been regularly used to assess orthostatic tolerance (Samueloff et al., 1966a; Wolthuis et al., 1970a; Sander-Jensen et al., 1986; Arbeille et al., 1995; Fortney et al., 1992; Smith et al., 1996) and consequently operational definitions of orthostatic tolerance, in which standing per se has taken no part in the experimentation, abound. Although some effects of standing are reproduced by these other methods, for example a caudal shift in blood, certain other effects are not reproduced and others specifically related to the method used may be introduced, which are not involved with the act of standing (Raven and Pawelczyk, 1993; Self et al., 1996). The possibility exists, therefore, that 'orthostatic tolerance' as measured by passive head-up tilt may not be identical to that measured during unassisted standing which in turn could differ from the responses derived from LBNP. A cross sectional comparison of how orthostatic tolerance is affected by exercise training may therefore be compromised if studies involving more than one method of assessing orthostatic tolerance are considered in unison.

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[1] The definition of a term specific to a given study, project or publication.

Separate definitions of orthostatic tolerance as measured by each mode might be required for clarity. This problem is illustrated by an examination of the results of 14 studies designed to investigate the question of whether orthostatic tolerance is related to fitness. Eight investigations utilised LBNP (Luft et al., 1976; Smith et al., 1988b; Convertino et al., 1990b; Levine et al., 1991; Stevens et al., 1992; Raven, 1993; Savard and Stonehouse, 1995; Raven et al., 1998) and six used either passive head-up tilt or standing (Klein et al., 1969a; Shvartz and Meyerstein, 1972; Convertino et al., 1984; Lansimies and Rauhala, 1986; Williamson et al., 1992; Shvartz, 1996). Data from six of the eight LBNP papers showed a significant adverse effect of endurance training on orthostatic tolerance, whilst the other two suggested an improved tolerance (Convertino et al., 1990b; Raven et al., 1998). Of the head-up tilt/stand papers, four showed no relationship, whereas two showed a positive relationship (Convertino et al., 1984; Shvartz, 1996). It might be concluded from the results of the LBNP studies that there may be an inverse relationship between orthostatic tolerance and endurance fitness, however, by examining only the head-up tilt/stand data no clear relationship is seen, whereas attempting to answer the question by considering all of the experimental data together leads to an inconclusive result.

A second confounding factor is that of inter-subject differences; i.e. control of test subject groups. Most prior work has involved cross-sectional analysis in which a group of 'fit' subjects is compared with an 'unfit' group. Although sample groups are usually matched to some degree the large number of factors that appear to be associated with orthostatic tolerance (e.g. phenotype, genotype, gender, age, health, mode of exercise training, number of years of training) virtually assures inadequate matching. Use of longitudinal studies overcomes this problem by means of test – retest comparison of the same subjects. A third confounding factor, however, is the level of fitness necessary for orthostatic tolerance to be adversely affected, it is likely that only the highly fit may be affected. What has not been ascertained is whether it is the exercise training per se or the inherent predisposition to be able to become fit that may be the critical factor related to orthostatic tolerance. With this in mind is it better to take highly-fit subjects and detrain them to examine the effect on orthostatic tolerance (and then maybe retrain them), or to 'train' normal-fit subjects not knowing whether they will be able to achieve a level of fitness sufficient to elicit an effect? Attempting to recruit competitive athletes or fitness professionals, on to a study in which

they are requested to refrain from exercise for a number of months, is very difficult. Consequently, few longitudinal detraining studies have been conducted and thus little highly controlled data suitable for an accurate assessment of the issue, exists.

The final confounding factor is the definition of fitness and how to assess it. It is fairly evident that if orthostatic tolerance is related to fitness it is to 'aerobic fitness' i.e. the ability to carry out moderately intensive exercise involving large muscle groups for long periods of time, as opposed to strength or power (Raven and Stevens, 1990; Geelan and Greenleaf, 1993; Cybulski et al., 1999). In fact forms of resistive training such as weight-training appear to improve orthostatic tolerance, whereas methods of training which comprise aerobic and resistance elements may have little effect overall (Lightfoot et al., 1994; McCarthy et al., 1997).

The classical method of obtaining a measure of aerobic fitness is to determine maximum oxygen uptake ($\dot{V}O_2max$). This assessment, although currently the 'Gold-standard' for assessing endurance capabilities and a very good measure of such, is not a perfect measure. For this reason although some quite strong relationships between orthostatic tolerance and $\dot{V}O_2max$ have been found (Luft et al., 1976; Williamson et al., 1992), other studies have shown either poor or no relationship (Shvartz and Meyerstein, 1972; Lansimies and Rauhala, 1986). Often the reasons for this may be due to the aforementioned confounding factors in addition to an imperfect relationship between $\dot{V}O_2max$ and aerobic fitness.

Clearly, therefore, despite a large quantity of research data examining the area of orthostatic tolerance and fitness, the multitude of different subject groups used, experimental designs and modes of assessments adopted and the different concepts of orthostatic tolerance assumed, make it difficult at present to derive a definitive answer to the question 'does endurance fitness affect orthostatic tolerance?'

2.2. RESPONSE TO ORTHOSTASIS

To address the problem correctly an understanding of what happens during orthostasis is required; in particular the mechanisms responsible for the physiological events leading to orthostasis induced syncope. Maintenance of appropriate blood flow to critical organs on assumption of the upright posture is a major physiological challenge. The act necessitates a multi-factorial response involving neural, hormonal and haemodynamic changes both as acute reflex and longer-term regulatory responses.

Response to Standing. Moving from supine to an upright stance typically takes 2-5 s (Borst et al., 1982; Sprangers et al., 1991a). The increase of the hydrostatic pressure gradient along the long axis of the body causes arterial pressure above the hydrostatic indifference point to fall. By +10 s post standing brachial arterial pressure may fall as much as 40 mmHg (Amberson, 1943). The subsequent unloading of arterial baroreceptors results in the withdrawal of vagal activity to the heart and thus increased cardiac inotropy and chronotropy. This effect in combination with the muscular effort of standing raises heart rate by about 30 bpm above that of supine (Ewing et al., 1980; Borst et al., 1982; Sprangers et al., 1991a; Sprangers et al., 1991c). This peak in heart rate occurs approximately 12 s after the initiation of standing (Ewing et al., 1980; Borst et al., 1982).

Standing leads to a drainage of approximately 650 ml of venous blood (Blomqvist and Stone, 1983) to dependent regions with a consequent reduction in venous return to the heart. The reduction in cardiopulmonary baroreceptor stimulation due to the resulting decrease in right heart filling leads after 12 s or so to a reduction of parasympathetic inhibition of sympathetic activity and thus increases in skeletal muscle, renal and splanchnic vasoconstriction combined with an arterial baroreceptor derived increase in sympathetic vasoconstriction (Zoller et al., 1972; Berdeaux et al., 1992). There may also be a transient increase in venoconstriction which may contribute towards supporting the circulatory system during the initial movement of blood to the lower body (Samueloff et al., 1966a). Systemic vascular resistance, therefore, increases concomitant with an increase in cardiac output[2] thus restoring arterial pressure to an acceptable level. As mean arterial and pulse pressures are restored, baroreceptor stimulation increases in both low and high pressure regions of the

[2] Also aided by restoration of venous return when dependent capacity vessels fill.

circulation resulting in a lowering of heart rate to about 5 bpm above resting levels (Sprangers et al., 1991c).

Despite an improved venous return, after 5 min stroke volume will be approximately 45% lower than that produced by the horizontal position (Ward et al., 1966). The cardio-acceleration initiated by the baroreceptors at this point, although increasing heart rate by about 35%, fails to fully sustain cardiac output which may still be 27% below the supine level (Amberson, 1943; Ward et al., 1966). Subsequent to the immediate, short term response to standing i.e. within 30 s, and as a result of a number of factors associated with the orthostatic condition (as discussed below) heart rate normally continues to rise thereafter at a rate of about +0.5 to 1.5 $bmp.min^{-1}$.

Rhythmic activity from the antigravity muscles occurs during quiet standing (Inamura et al., 1996). The muscle pump mechanism derived from this activity appears to be linked with rhythmic myogenic contractions in the lower body vasculature with a frequency of 1 Hz which propel blood through the venous system towards the heart (Inamura et al., 1996). These actions in combination with the cyclic changes in intrathoracic pressure produced by respiration, act as effective aids to venous return and thus obviate to some degree the adverse effect of hydrostatic pressure on stroke volume. In spite of the effectiveness of the these aids the increased arterial pressure in dependent regions results in an alteration of the Starling equilibrium within the capillaries such that fluid is filtered out into interstitial tissue (Amberson, 1943). The gradual extravasation which occurs as standing continues leads to a plasma reduction of 15% to 25% (Lundvall and Lindgren, 1998) after 14-30 min (Davies et al., 1976; Jacob et al., 1998b) and increased plasma protein concentration, haematocrit and colloidal osmotic pressure (Lundvall and Lindgren, 1998). Venous return, already compromised by the hydrostatic gradient, slowly decreases as blood volume is reduced and viscosity increases thus adversely affecting stroke volume. The reduced right heart filling and relatively low carotid sinus arterial pressure cause a diminution of baroreceptor activity which act jointly to increase peripheral resistance through increased venous and arteriolar tone, to counter the falling arterial pressure. The continuous, albeit gradual, loss of blood volume and increasing blood viscosity compromise venous return to the heart and arterial pressure for as long as standing continues.

Raised plasma adrenaline and noradrenaline concentrations are detectable from as early as 2 to 3 min of standing due to the activation of the sympathetic nervous system (Jacob et al., 1998b). By 10 to 20 min plasma concentration of noradrenaline may be increased by 200% (occurring notably at the time of greatest rate of plasma volume loss), but subsequently levels off (Jacob et al., 1998b). The noradrenaline response to hypovolaemic stress in contrast to that of adrenaline either declines after the initial action of standing returning to baseline levels after 30 to 40 min[3] or remains only slightly elevated throughout (Sander-Jensen et al., 1986). As orthostasis continues a brief surge in adrenaline concentration may be noted immediately prior to syncope, stabilising or even decreasing during the vasovagal response (Lieshout et al., 1991). Orthostasis induced hypovolaemia may be responsible to a large degree for the early increase in plasma adrenaline (Jacob et al., 1998b); however, adrenaline levels have been seen to markedly increase during syncope to levels such as 250 $pg.ml^{-1}$ (Sander-Jensen et al., 1986). The β-adrenergic dilatation, which may result from high plasma adrenaline concentrations, could oppose the vasoconstriction required to maintain adequate arterial pressure during the central hypovolaemia (Lieshout et al., 1991) and might therefore may be considered a contributory factor for the syncope.

The general increase in sympathetic activity associated with orthostasis leads to an increase in renal vascular tone and reduced glomerular filtration rate. Heightened renal sympathetic activity in combination with decreased atrial filling induced by the upright position result in increased plasma renin activity (PRA) by 60% to 300% (Davies et al., 1976; Jacob et al., 1998b) followed by elevated angiotensin II levels. The rise in PRA mirrors plasma volume reduction over the course of 30 min or so, decreasing slightly as plasma volume depletion levels off (Davies et al., 1976). Consequently, from about 5 min post standing a powerful ∝-adrenergic stimulation derived from angiotensin results in a humorally induced increase in tubular Na^+ reabsorption and direct constriction of peripheral vascular smooth muscle which further aids the maintenance of arterial pressure and which may in fact often lead to a slow, mild increase in diastolic pressure over approximately 45 min (Jacob et al., 1998b). Initially; i.e. before any signs or symptoms of pre-syncope, cardio-acceleration, a gradual increase in

[3] An observation associated with the plateauing of overall sympathetic activity at this stage, with the exception of that of the adrenal medulla (Sander-Jensen, 1991).

peripheral resistance, venoconstriction and humoral/renal induced anti-diuresis are able to maintain mean and pulse pressure within acceptable limits.

Further to these mechanisms of maintaining arterial pressure, increased concentrations of plasma arginine vasopressin (AVP) are produced as a result of orthostatic stress (Segar and Moore, 1968). Upon standing unloading of cardiopulmonary and arterial baroreceptors results in decreased vagal afferent activity subsequent to an increase in efferent sympathetic activity (Dietz et al., 1997). Acute baroreceptor unloading results in diminished atrial natriuretic peptide formation and thus augmented AVP release (Brenner et al., 1990; Persson, 1996). A drop in atrial natriuretic peptide concentration results in decreased inhibition of AVP synthesis and thus raised plasma AVP levels. This initial increase in plasma AVP concentration is in the region of 100 – 200% occurring within 30 min of standing (Davies et al., 1976). During this phase of the AVP response plasma concentrations steadily rise until values of ~20 $pg.ml^{-1}$ are achieved (Aylward et al., 1986; Simpson et al., 1986). At moderately low physiological concentrations AVP primarily promotes water reabsorption as a means of defending plasma volume (Davies et al., 1976; Aylward et al., 1986). AVP concentrations of this magnitude have little effect on sympathetic activity or mild perturbations of baroreceptor function (Goldsmith, 1994), however, a second more profound rise is often seen when the maximum decrease in effective circulating blood volume has occurred. By this point; i.e. after 20 to 30 min in the erect position, plasma AVP concentration has been reported to have increased by a factor of 7 to 15 (Segar and Moore, 1968; Davies et al., 1976). Despite the small change in plasma volume between +15 and +30 minutes, a threshold is probably reached which triggers the second surge in AVP secretion (Davies et al., 1976). A continuing rise in plasma AVP may occur despite a stabilisation of plasma osmolality (Jacob et al., 1998b) suggesting that the stimulus for the second stage in secretion may be derived from the unloading of cardiac and/or arterial receptors.

As orthostasis continues, the reduction of central blood volume causes a continued reduction in the activation of cardiac and arterial mechanoreceptors as a result of reduced cardiac filling and diminished arterial pulse pressure (Sander-Jensen et al., 1987). Although mean arterial pressure can be maintained in the face of these perturbations an as yet unidentified threshold is ultimately passed which leads to a profound decay in systemic peripheral resistance and thus syncope (Fritsch-Yelle et al., 1996; Norsk, 1996). The primary

mechanism responsible for the syncopal episode appears to be an intense peripheral arteriolar vasodilatation produced by the reduced sympathetic outflow to arterioles in skeletal muscle (Sander-Jensen et al., 1986; Sander-Jensen et al., 1987; Dietz et al., 1997) although it has been conjectured that an active sympathetic dilatation mechanism might also be involved (Barcroft and Edholm, 1945; Dietz et al., 1997). With the loss of sympathetic tone comes a profound reduction in total peripheral resistance, mean arterial pressure, pulse pressure and therefore inadequate cerebral perfusion. The acute changes in central blood volume and pulse pressure are probably responsible for a dramatic rise in plasma AVP at or during vaso-vagal syncope (Davies et al., 1976; Norsk et al., 1993; Norsk, 1996).

Response to Head-up Tilt. With the exception of two principle differences head-up tilt can be considered to be equivalent to the upright posture. Head-up tilt differs to standing as a result of the lack of use of most of the postural anti-gravity muscles and the angle of effect of gravity (Sprangers et al., 1991c). Providing waist and knee straps are used which do not impede blood flow, head-up tilt can be imposed without the use of the leg muscles thus enabling the relaxation of the postural muscles and eliminating the beneficial effects of the muscle pumps. The angle of tilt is insufficient to produce a hydrostatic gradient equivalent to that extant when standing (135 mmHg difference between head and feet[4]) but can produce a gradient close to that of standing (70 ° head up tilt = 125 mmHg between head and feet). The use of 70 ° as the angle for head-up tilt provides a stress which in most cases is greater than that of standing, however the difference may not be significant for some subjects (Hyatt et al., 1975).

The similarity between standing and head-up tilt is such that for the purpose of this study both forms of stress will be considered the same.

Response to Lower Body Negative Pressure. As with standing, progressive LBNP to levels sufficient to severely stress the cardiovascular system (>50 mmHg) increases heart rate (28 to 40 bpm) (Baily et al., 1991; Norsk et al., 1993; Chang et al., 1994), decreases stroke volume (-50%) (Norsk et al., 1993; Chang et al., 1994) and reduces cardiac output (12% to 17%) (Norsk et al., 1993; László et al., 1998). The observation that central venous pressure falls to zero and systemic and forearm vascular resistance increases by up to 100% before

[4] For a height of 180 cm.

any significant change in mean arterial pressure or heart rate occurs, might suggest that activation of sympathetic vasoconstriction occurs in the absence of a significant reduction in stimulation to the sinoaortic receptors and may be principally as a result of unloading the cardiopulmonary baroreceptors (Gilbert and Stevens, 1966; Johnson et al., 1974). Jacobsen and colleagues (1993) and Norsk and co-workers (1993) however, indicate that should reductions in pulse pressure occur, the arterial baroreceptors also significantly contribute to the orthostatic response.

Gilbert and Stevens (1966) examined the effects of 80 - 90° head-up tilt and 60 mmHg LBNP and concluded that the mean arterial pressure responses were similar, however, 60 mmHg LBNP was far more stressful than head-up tilt, requiring 50% additional total peripheral vascular resistance to maintain mean arterial pressure. Musgrave and co-workers (1969, 1971) examined the cardiovascular responses to and fluid redistribution caused by LBNP. He measured a 614 ml increase in fluid volume in the legs at –40 mmHg and an augmentation of capillary filtration to the interstitium. Musgrave suggested that the heart rate and arterial pressure changes produced by 40 to 50 mmHg LBNP were equivalent to those produced by 70° head-up tilt.

Differences Between Head-up Tilt/Stand and LBNP Responses. Although cardiovascular and neuroendocrine responses to LBNP appear very similar to those of standing and head-up tilt, principle differences exist as a result of the postures adopted and the manner in which central hypovolaemia is affected. The stress imposed upon the body during 'orthostasis' initiates a number of responses designed to maintain arterial pressure, the mechanisms of which can be divided into acute reflex responses and chronic neuroendocrine responses. With regards to the former, head-up tilt and standing result in a reduction of arterial baroreceptor stimulation due to the change in hydrostatic pressure, whereas the retention of the supine posture during LBNP maintains a higher degree of arterial baroreceptor loading. Consequently, the initial baroreceptor derived increase in heart rate seen during standing does not occur during LBNP.

Furthermore, reflex responses to decreased stimulation of cardiopulmonary baroreceptors occur in a step-wise manner during progressive LBNP, but during head-up tilt/stand the gradual reduction in mean arterial and pulse pressures elicit a gradual decrease in stimulation. As will be discussed shortly, acute changes in baroreceptor stimulus elicit a

dynamic response from the receptors whereas gradual alterations elicit a slow adaptation of response, the reflex efferent profile of which is different from that of the dynamic. The indication that arterial baroreceptors may play a more dominant role in the regulation of arterial pressure during orthostasis than the cardiopulmonary baroreceptors (Jacobsen et al., 1993; Norsk et al., 1993), highlights the possibility, therefore, that in view of the differences between the LBNP and head-up tilt/stand postures, substantially different afferent baroreceptor activity may occur during 'orthostasis' with potentially different efferent responses. Furthermore, during supine LBNP the beneficial effect of the leg muscle pumps is lost thus exacerbating the reduction in venous return to the heart.

During LBNP the reduction of pressure acts upon all points of the lower body equally and in all directions. This effect is likely to be the principle reason why LBNP in excess of 40-60 mmHg has been reported to be more stressful than the stress imposed by head-up tilt or standing (Gilbert and Stevens, 1966; Musgrave et al., 1969; Musgrave et al., 1971). The fact that the final negative pressures reached at the point of pre-syncope during progressive LBNP are in the region of 70 to 120 mmHg (Bondar et al., 1994; Lightfoot et al., 1994; White and Gotshall, 1994; Convertino, 1998a) indicates that progressive LBNP may be considerably more stressful then head-up tilt or standing. As the effective activation of, and response to, the principle hormones, AVP and renin-angiotensin is time dependent, the effectiveness of the neuroendocrine system very much depends upon the time course of the stress involved (Carroll et al., 1995).

Mild non-hypotensive LBNP exerts little influence on plasma AVP or adrenaline levels (Goldsmith et al., 1982; Norsk et al., 1993). As pulse pressure is reduced and thus arterial baroreceptors unloaded, however, AVP, PRA and noradrenaline levels substantially increase by 200%, 311% and 40% respectively (Goldsmith et al., 1982; Norsk et al., 1993). The effectiveness of AVP in the control of arterial pressure appears to be minimal over short periods of time when concentrations are moderate (< 50 $pg.ml^{-1}$), although when plasma concentrations become very high (> 200 $pg.ml^{-1}$) a vasoconstrictor effect has been reported, however, at extremely high concentrations the finding that forearm vasodilatation occurs appears inappropriate (Aylward et al., 1986). As with AVP, the action of PRA is insufficient to act significantly upon vascular control during mild to moderate orthostatic stress (Bevegård et al., 1977), however, should plasma volume and osmolality be significantly reduced both AVP and PRA exert noticeable influences to defend blood volume by means of

anti-natriuresis and anti-diuresis (Aylward et al., 1986; Jacob et al., 1998b). Consequently, the time dependences of these hormones may be as a result of the time required to affect plasma volume and osmolality, in which case longer duration orthostatic stress such as that imposed by head-up tilt, will elicit a greater contribution to orthostatic tolerance from the neuroendocrine system than would be the case for shorter more rapidly imposed stress such as that produced by LBNP. A larger contribution towards the maintenance of homeostasis may therefore be derived from the neuroendocrine system during head-up tilt than progressive LBNP because the orthostatic challenge is less stressful and thus can be 'endured' for a longer duration.

In summary, therefore, the cardiovascular and neurohumoral responses of mild to moderate LBNP appear to be similar in magnitude and effect to those of the upright posture, however, the profiles of baroreceptor derived efferent activity may differ between these methods and severe LBNP in excess of 60 mmHg appears to impose much greater demands on the cardiovascular system than standing/head-up tilt.

2.3. MEASURING 'ORTHOSTATIC TOLERANCE'

The ability to withstand orthostatic stress has been investigated by examination of the responses to standing (Hyatt et al., 1975; Bjerkhoel and Lundvall, 1994; Whitson et al., 1995), head-up tilt (Sander-Jensen et al., 1986; Patwardhan et al., 1995; Kikushima et al., 1999) and LBNP (Vroman et al., 1988; Convertino et al., 1993; Arbeille et al., 1995). The principle effect of the adoption or application of each of these conditions is an acute caudal movement of body fluids (Hyatt et al., 1975; Samueloff et al., 1966a; Sather et al., 1986). The adequacy of subsequent reflex and neurohormonal adaptations to the 'stress' provides the measure of orthostatic tolerance under investigation. The quantification of orthostatic tolerance varies, but it is now generally regarded that accurate assessment can only be ascertained if the point of pre-syncope is achieved (Convertino, 1993). The identification of imminent circulatory collapse due to orthostatic stress is slightly different between methods, however, all elicit signs such as pallor, excessive perspiration and symptoms such as lightheadedness, dizziness and nausea prior to syncope (Allen et al., 1945; Sather et al., 1986; Sander-Jensen, 1991; Fortney et al., 1992). The common use of non-invasive blood

pressure measurement devices such as Finapres, has made the identification of other warning signs relatively easy. A clear precipitous drop in arterial pressure combined with an acute bradycardia is usually observed immediately prior to syncope, thus providing an easily identifiable end point (Self et al., 1996; Smith et al., 1996; Jardine et al., 1997).

2.3.1 *Stand Test.* The purpose of orthostatic tolerance assessment is to determine the capability to withstand the stress of orthostasis, in which case the use of a test involving the upright posture appears to be the most specific method. The effects of standing have been examined in detail since the 19th century (Hill et al., 1897; Crampton, 1920; Amberson, 1943; Ward; Ward et al., 1966). Despite the appropriateness of this method there are two aspects which often preclude its use, the first being subject safety. Active standing requires muscular control from the subject to maintain the stance. At syncope muscular control is lost (Lieshout et al., 1991) and thus standing does not offer a safe method of lowering the subject to horizontal should fainting occur. Investigators have adapted the standing posture such that the subject places the back of the shoulders against a wall with his/her heels approximately 15cm from the wall (Hyatt et al., 1975). This position provides some support in the event of a faint.

The second problem with the stand test is the duration required to reach pre-syncope. Although the test may precipitate a pre-syncopal end point in as little as 5 min for deconditioned subjects (Fritsch-Yelle et al., 1994; Buckey et al., 1996b), standing for longer than 60 min is often required for healthy subjects and thus it cannot be considered a rapid procedure (Davies et al., 1976). For these reasons the stand test is considered by some to be inappropriate to induce a pre-syncopal end point (Convertino, 1998a).

2.3.2 *Head-up Tilt.* The natural progression from the stand test is the provision of a tilting platform to which the subject can be secured, thus improving safety in the event of syncope by means of a controlled return to horizontal. Furthermore, the use of chest and knee straps (Sprangers et al., 1991b; Evetts and Russomano, 1995) or a saddle (Vogt, 1967) enables the subject to adopt a near vertical position with minimal muscular effort. 'Head-up tilt' therefore enables relaxation of the anti-gravity muscles, minimising the pumping action of the leg muscles, which normally aid venous return to the heart and thus circulatory

insufficiency will occur earlier than for active standing (Belkaniya, 1981; Shamsuzzaman et al., 1998).

The response to the angle of head-up tilt used has been examined indicating that 70° may be optimal (Tuckman and Shillingford, 1966; Hainsworth and Al-Shamma, 1988; Sprangers et al., 1991b). Although the head-up tilt test is an improvement on the stand test it typically takes 3 to 6 s for a tilt-table to be returned to horizontal from 70° and thus the adoption of the horizontal recovery position is slow (Shvartz, 1968; Sprangers et al., 1991b; Evetts and Russomano, 1995). Despite the reduction in test duration required for subjects to reach pre-syncope the mean tilt-test time to pre-syncope was 26 min for the subjects of Vogt (1967) and many subjects may still not reach this point within 60 min.

2.3.3 *Lower Body Negative Pressure.* The adoption of LBNP by NASA as a means of assessing orthostatic tolerance has been primarily due to the fact that the gravity vector is not required and thus examination of tolerance in a weightless environment is possible. Further to this, the subject can remain in the horizontal position thus overcoming the safety concerns mentioned above. LBNP can also be stopped in less than a second by disconnecting the suction source from the LBNP chamber, thus providing an immediate return of blood to the central circulation; and because the severity of LBNP can be accurately controlled, pre-syncope can be reached in almost all subjects within 30 min (Stevens et al., 1992; Lightfoot et al., 1994). In a comparison of the techniques of head-up tilt, standing and LBNP, Hyatt and co-workers (1975) concluded that although all three techniques were able to assess orthostatic tolerance, LBNP appeared to be the most sensitive tool.

The LBNP protocols used in orthostatic tolerance assessment vary considerably. Since the work of Wolthuis and colleagues (1970a, 1970b), however, a progressive, incremental format has been adopted as the most suitable design although agreement as to what pressures and durations should be used does not exist and thus no single protocol is recognised as the standard as yet. The usefulness of progressive LBNP as a method depends upon the ability to accurately detect the subject's orthostatic tolerance (Wolthuis et al., 1970a) i.e. the sensitivity of the method. As the degree of negative pressure rather than duration appears to be the governing factor for tolerance (Wolthuis et al., 1970b) and because the inter-individual variation in tolerance to progressive LBNP is high (Wolthuis et al., 1970a; Luft et

al., 1976; White and Montgomery, 1996), the choice of protocol for a heterogenous group of individuals should include small incremental changes in pressure for only short periods. The choice of LBNP protocol for this study, therefore, was one which comprises a 10 mmHg reduction of chamber pressure every 3 min to pre-syncope (Kuriyama et al, 1997; Lightfoot et al, 1994; Watenpaugh et al, 1994).

2.3.4 *Combined Orthostasis and Lower Body Negative Pressure.* The combination of the upright posture and LBNP has been used in research and clinical practice to provide an effective means to impose hypotensive stress without the loss of the hydrostatic gradient inherent in head-up tilt and stand tests (Newberry et al., 1970; Polese et al., 1992; El-bedawi and Hainsworth, 1994; Mtinangi and Hainsworth, 1998; Imms, 1999). Although the combined use of both procedures offers a method which enables a pre-syncopal end-point to be attained more rapidly than head-up tilt or standing (mean of 9 min - Newberry et al., 1970), the method has not as yet been widely adopted. This may be due to the difficulty in comparing results of studies employing LBNP or head-up tilt/stand with those using the combined method and/or due to the challenges of developing a LBNP chamber which can be safely pivoted to 60° or 70°. Although the magnitude of physiological stress involved with combined LBNP/head-up tilt appears greater than the other methods used singularly, the measured physiological responses appear to be similar in magnitude to those observed during LBNP (Polese et al., 1992; El-bedawi and Hainsworth, 1994).

2.4. THE HUMAN BAROREFLEX SYSTEM

The mechanisms by which orthostatic control is achieved and maintained essentially consist of elements that detect and report change, a central network that assimilates and assesses the afferent information, followed by actions that effect a response to that change, which are then detected again by the receptors i.e. negative feedback mechanisms. The baroreflex system is one of the most important human physiological control mechanisms because of the rapidity in which it brings about change in autonomic function to maintain blood supply to the brain during postural change.

The function of the baroreflex is to detect rapid changes in circulatory volume and pressure and elicit equally rapid autonomic responses to counteract the changes in an attempt

to maintain normal working volumes and pressures. Baroreflex responses are derived from a complex interaction of the actions from a number of receptor groups. The baroreceptor groups lie in the carotid sinuses, thin walled dilatations at the origin of the internal carotid artery on either side of the neck; in the adventitia of the aortic arch and within the walls of the cardiac chambers, at the veno-atrial junctions of the heart and in the pulmonary arteries. Fig 2.1 illustrates the locations and neural efferent and afferent pathways.

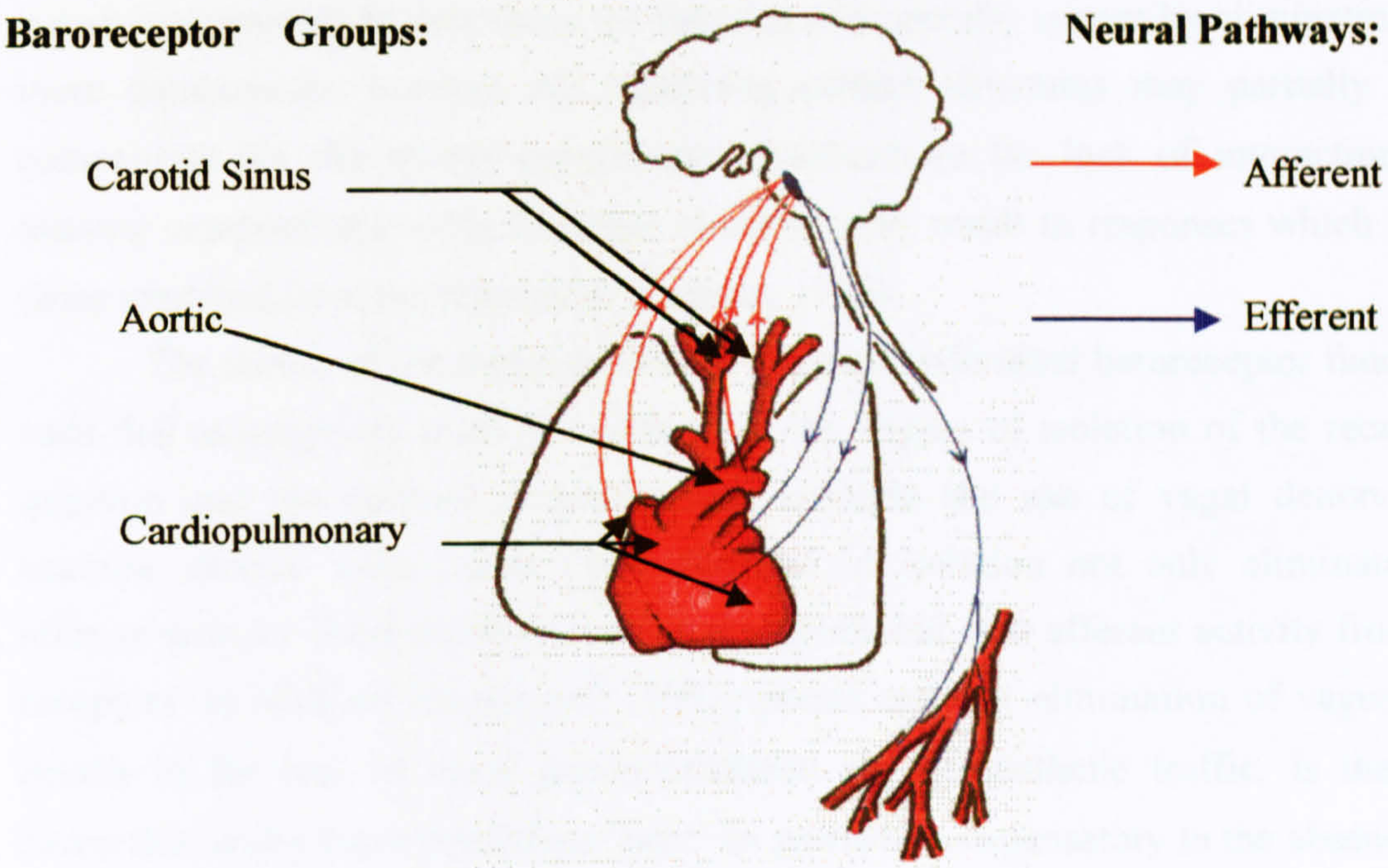

FIGURE 2.1 BARORECEPTOR GROUPS AND NEURAL PATHWAYS

The receptor groups are generally categorised as arterial (carotid and aortic) and cardiopulmonary (cardiac, pulmonary and veno-atrial) receptors. The arterial receptors are essentially mechanoreceptors which are stimulated by stretch of the arteries in which they lie usually as a result of increased arterial blood pressure. The cardiopulmonary receptors are also mechanoreceptors which due to their location accurately monitor changes in volume of the heart and thus signal cardiac filling.

2.4.0. *Assumptions Regarding Arterial and Cardiopulmonary Baroreflexes.* Although baroreceptor groups are conventionally described as either 'arterial' or 'cardiopulmonary' the distinction is not absolute. For example Hainsworth (1991) suggests that left ventricular and certain coronary vessel receptors may function as arterial baroreceptors in that they detect arterial pressure through its effect on ventricular and coronary perfusion pressures. Certainly the sum of the individual cardiac and pulmonary receptor group responses does not necessarily equate to the reflex responses derived from alterations in cardiac filling pressure. Persson (1996) in his review of cardiovascular control mechanisms and their interactions points out that it is not always possible to determine the function of a specific system by eliminating one or more components, because the remaining control structures may partially or fully compensate for the absent components. Furthermore the lack of interaction of the missing component(s) with the other elements may result in responses which differ to those expected from the remainder (Persson, 1996).

The nature of the methods used to examine individual baroreceptor function are such that assumptions must be made as to the degree of isolation of the receptors in question and the derived responses. For example the use of vagal denervation to examine carotid sinus baroreceptor function in isolation not only eliminates vagal afferent activity from cardiopulmonary receptors, but also afferent activity from aortic receptors. In addition Hainsworth (1991) points out that elimination of vagus control results in the loss of vagal parasympathetic and sympathetic traffic. Is the carotid baroreflex under these conditions 'pure' or partially compensatory in the absence of the other components? Indeed it has been proposed that the use of methods such as mild LBNP (suction < 20 mmHg) to unload 'cardiopulmonary' baroreceptors leads to altered stimulus to carotid baroreceptors through changes in carotid artery diameter despite a lack of significant change in mean arterial or pulse pressures[⊕] (Lacolley et al., 1992).

Bearing in mind the points outlined above the assumptions maintained in this thesis are firstly that attempts to examine individual baroreceptor group function in isolation derive responses which are predominantly those of the receptor group in question and secondly that although the exact nature of the influences which produce the baroreflex response to altered cardiac filling have not been quantified the common use of the term 'cardiopulmonary baroreflex' is acceptable and is used to refer to those responses derived from the interaction of all receptor groups affected by altered cardiac filling.

[⊕] although actual changes in carotid sinus diameter and baroreceptor activity were not measured.

2.4.1 ARTERIAL BARORECEPTOR FUNCTION.

A rise in arterial pressure causes arterial distension and thus stimulation of myelinated and un-myelinated nerve endings at the media-adventitia borders of the carotid sinuses and aortic arch (Heymans and Neil, 1958; Eckberg and Sleight, 1992). The receptors respond to the stretch of the arteries, and thus the degree of deformation and the rate of resultant impulses are a function of transmural pressure. The afferent pathway of the carotid receptor group comprises rapidly conducting myelinated afferent fibres in the carotid nerve which pass to the glossopharyngeal nerve (IXth cranial nerve), terminating at the nucleus tractus solitarius in the medulla (Sun and Guyenet, 1987). The aortic receptors afferent pathway also passes to the nucleus tractus solitarius, but by way of the vagus (Xth cranial nerve) (Sun and Guyenet, 1987).

A rise in arterial transmural pressure stimulates the baroreceptors resulting in an increase in the rate of firing. The heightened afferent flow to the nucleus tractus solitarius results in an integration of neural activity primarily at this site but also at sites in the rostral ventrolateral medulla (Sun and Guyenet, 1987). Mono- and polysynaptic interneural connections between these areas and efferent sympathetic and vagal nuclei at the nucleus ambiguous and the dorsal motor nucleus, lead to reflex efferent traffic to the heart and systemic vasculature, thus effecting a response (Bronk and Stella, 1932; Donoghue et al., 1984).

Static and Dynamic Response. Increased transmural pressure resulting from a rise in arterial pressure causes a transient burst of action potentials as the arterial wall stretches. This 'dynamic response' is indicative of the rate of change of pressure and is evident as a result of the change in pressure which occurs during the arterial pressure wave even when mean arterial pressure is constant (Downing, 1960). The dynamic response reduces as the rate of change subsides, leveling off at a new sustained rate of firing, higher than the previous rate (the adapted response), signaling the new arterial pressure (Coleridge et al., 1987). In a similar manner arterial baroreceptor activity transiently falls silent when arterial pressure drops, restarting neural activity at a lower rate as arterial pressure levels off (Landgren, 1952; Kirchheim, 1976).

Threshold and Range of Firing. Kirchheim (1976) in his comprehensive review of baroreceptor structure and function reports that large baroreceptor myelinated 'A' fibres detect pressure changes above an arterial pressure of approximately 50 mmHg and respond maximally at about 90 mmHg. Whereas the more numerous un-myelinated 'C' fibres are activated at a higher threshold (approximately 120 mmHg) and respond maximally above about 160 mmHg. Although the response of each fibre appears to be moderately limited, i.e. they can respond over a range of approximately 30 mmHg, because the nerve trunk possesses a variety of 'A' and 'C' fibres a large range of arterial pressure changes (possibly 150 mmHg) can be detected and responded to (Kirchheim, 1976).

Response to Pulse Pressure. The combination of dynamic sensitivity and activation of high threshold receptors enables the carotid baroreceptors to be sensitive to arterial pulse pressure. Oscillations in arterial pressure result in a relatively greater contribution from the dynamic response than from the adapted, thus causing a greater aggregate afferent activity in the carotid sinus nerve trunk (Ead et al., 1952). This affect is less and may even be absent, however, when pulsatility occurs at very high arterial pressures (Koushanpour and McGee, 1969).

Response to Change in Arterial Pressure. Increased stimulation of the arterial baroreceptors by means of stretch of the arterial walls promotes cardiac vagal activity and reduced sympathetic activity to the heart and peripheral vasculature thus reducing cardiac rate and inotropy (Bevegård and Shepherd, 1966; Mitchell and Victor, 1996) and in vasoconstrictor tone. The resulting decrease in vascular resistance in combination with the bradycardia lowers arterial pressure.

A reduction in stimulation of the baroreceptors by means of reduced arterial pressure, leads to decreased receptor firing. The reduced afferent input promotes a decrease parasympathetic inhibition of sympathetic activity to the heart, resulting in an increase in heart contractility and rate. An augmentation of efferent sympathetic activity to skeletal muscle (Rea and Eckberg, 1987), renal and splanchnic vascular beds and to some degree the skin, raises systemic vascular resistance.

2.4.2 CARDIOPULMONARY BAROREFLEX FUNCTION.

A network of baroreceptor afferent fibres innervates the heart and pulmonary artery. Overall, these have a tonic inhibitory effect on heart rate and vascular tone. There are essentially two categories divided according to function. The first are the mechanoreceptors situated around the veno-atrial junctions, connected to myelinated vagal fibres (Mancia and Donald, 1975). The second group consists of mechanoreceptors scattered throughout the atria, ventricles and pulmonary artery, served by non-myelinated fibres in the vagus and cardiac sympathetic nerves (Shepherd and Abboud, 1983).

Response to Change in Cardiac Stretch. The seminal work of Roddie, Shepherd and Whelan (1957) showed that stimulation of receptors in the area of the heart and pulmonary vasculature lead to skeletal muscle vasodilatation. The association between change in central blood volume and vasodilatation was independent of arterial pressure change. Activation of the veno-atrial group causes tachycardia through a selective sympathetic excitation, whereas activation of the second diffuse group leads to increased vagal afferent traffic subsequent to reduced sympathetic efferent traffic and thus bradycardia and peripheral vasodilatation (Cornish et al., 1989; Shi et al., 1997). Therefore, cardiac filling is monitored and aided through antagonistic responses by these two receptor groups.

Overall these reflexes have a depressor effect. The cardiopulmonary group as a whole is effective in response to small pressure changes in the low-pressure venous circulation and may detect small changes in intrathoracic blood volume when arterial pressure is unchanged. A relatively small decrease in cardiac filling pressure such as that induced by 15 mmHg LBNP is sufficient to elicit a measurable increase in muscle sympathetic nerve activity (Jacobsen et al., 1993).

Humoral Responses to Orthostasis. Increased sympathetic traffic to the splanchnic region resulting from hypotension leads to secretion of adrenaline by the adrenal medulla (Sander-Jensen et al., 1987). Adrenaline stimulates heart rate and contraction thus augmenting cardiac output. Heightened sympathetic activity increases arteriolar constriction reducing capillary pressure and altering the Starling equilibrium such that interstitial fluid moves into the blood plasma (Lote, 1987). The angiotensine-aldosterone system is activated by the

heightened renal sympathetic activity and thus vascular contraction and retention of electrolyte and water is promoted (Jacob et al., 1997).

Conversely, increases in blood volume and osmolality lead to humorally induced diuresis and natriuresis (Norsk, 1996). Some atrial myocardium cells secrete atrial natriuretic peptide in response to stretch, resulting in atrial natriuretic peptide induced natriuresis and diuresis (Brenner et al., 1990; Andersen et al., 1995) and inhibition of AVP release and thus reduce the AVP derived anti-diuresis and vascular constriction (Abboud and Thames, 1983). The combination of these responses therefore acts to decrease plasma volume and lower arterial pressure.

2.4.3 MEASURING HUMAN BARORECEPTOR FUNCTION

Carotid Baroreflex Function

Neck Chamber/Collar. In 1957 Ernsting and Parry used a Perspex box to examine the effects of reducing pressure around the neck. The pressure within the Perspex box was rapidly reduced effectively increasing transmural pressure across the walls of the arteries in the neck and thus stimulating the receptors of the carotid sinuses. The result was a transitory bradycardia and a sustained fall in arterial pressure whilst the suction was applied (Ernsting and Parry, 1957). Eckberg adopted Ernsting and Parry's concept, producing a smaller, slightly more refined lead 'collar' (Eckberg et al., 1975) and examined the technique during the 70s in sufficient detail to be able to ascertain the optimal method for stimulating the carotid sinus. A number of investigators have since modified the technique and produced variants of the collar concept (Stegemann et al., 1974; Ludbrook et al., 1977; Doerr and Convertino, 1989). Currently the most advanced system is probably that used by NASA based on the Eckberg technique, but using a silicon rubber collar (Sprenkle et al., 1986).

Paired Neck Chambers. Examination of unilateral carotid sinus responses has been successfully undertaken by introducing a division into a lead collar (Williamson and Raven, 1994). Successful investigations of carotid baroreceptor function have also been made using separate chambers placed over the area of each carotid sinus (Bauernfeind et al., 1985; Tafil-Klawe et al., 1990; Kelly et al., 1996). Of these studies only Kelly and co-workers compared their devices against the Eckberg collar, showing that although they were unable to produce

responses as great as those elicited by the lead collar, they were able to successfully examine the responses to neck pressure using this technique. With regards to unilateral response of the carotid sinuses, Bauernfeind and associates (1985) and Williamson and Raven (1994) found no difference between right and left responses whereas Tafil-Klawe and associates (1990) produced results suggesting that the right sinus may have a greater gain than the left.

Carotid Sinus Stimulation. Significant and incremental slowing of the heart (mean R-R increases of 278 to 485 ms) was recorded when pressures between –5 and –60 mmHg were applied to the neck using a lead collar (Eckberg et al., 1975). The degree of resulting R-R interval change elicited by the stimulation (lasting approximately 15 s) was reported to be dependent upon the timing of the suction. In a follow-up study Eckberg examined the effects of application of neck suction at different times relative to the heart's QRS complex (Eckberg, 1976). By applying numerous stimuli relative to the 'P' wave[5] it was observed that stimulation approximately 0.75 s before the next anticipated P wave produced the optimal response (Figure 2.2).

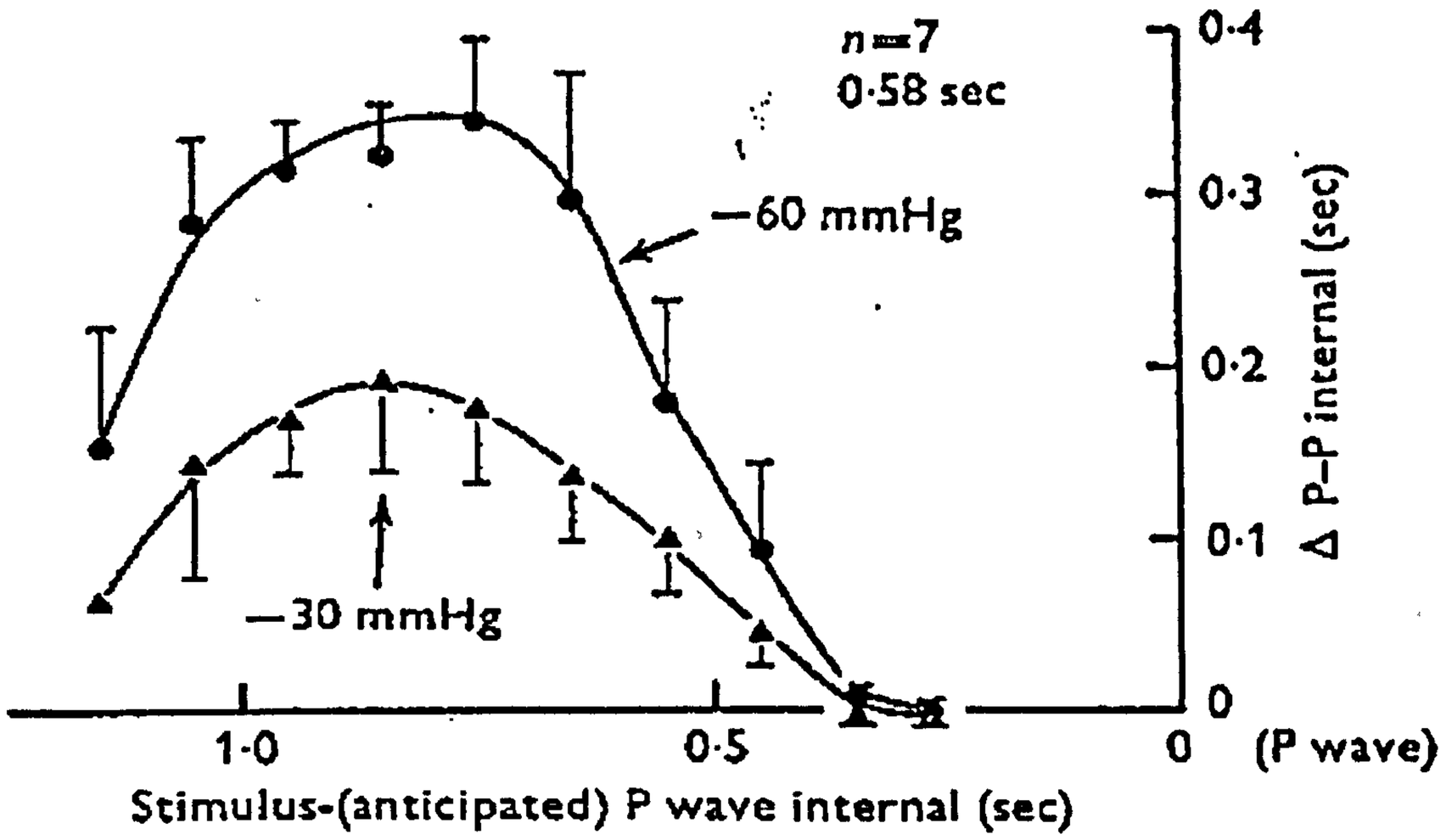

FIGURE 2.2 OPTIMAL TIME OF STIMULATION OF CAROTID SINUS RELATIVE TO ECG 'P' WAVE. Paired responses of 7 subjects to neck suction at –30 mmHg or – 60 mmHg for 0.58 s. Abscissa shows the time in advance of the imminent P wave the stimulation was applied (Eckberg, 1976).

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[5] Termed the 'anticipated P wave', because the timing of the P wave after the stimulus would be delayed by the stimulus.

Examination of the effect of duration of stimulus indicated that stimuli 0.58 s long elicited greater R-R interval slowing than shorter applications (Eckberg, 1976; Eckberg, 1977b) and yet were not so long as to produce interference from other reflex effects such as changes in vascular resistance (Eckberg, 1977b; Archer et al., 1979). Pressure application at rates of between -100 $mmHg.s^{-1}$ and –1800 $mmHg.s^{-1}$ were applied producing R-R interval responses which indicated that application rates in excess of –400 $mmHg.s^{-1}$ were necessary for optimal stimulation (Eckberg, 1977a). Eckberg suggested that such rates were necessary in order to approximate the naturally occurring rate of change of human arterial pressure which is in the region of –440 to –1200 $mmHg.s^{-1}$ (Mason et al., 1964). Archer and colleagues (1979) investigated the responses and effects derived from multiple stimuli (1 to 5 stimuli of 0.6 s) over 10 s. They concluded that the efferent response from one stimulus could persist for 3 s post application and that the duration of altered sinus node function for multiple stimuli could be up to 7 s. Eckberg and colleagues (1980) also found that stimulation during late inspiration or early expiration provoked optimal responses and that at normal respiratory rates baroreflex responses in expiration were greater than during inspiration. By adapting the neck collar so that positive pressure can be applied to the neck the full range of baroreceptor activity can be ascertained in which a sigmoid relationship between R – R interval and neck pressure is observed (Fritsch et al., 1992).

Cardiopulmonary Baroreflex Function

Examination of the effects of varying central blood volume upon skeletal muscle blood flow offers insight in to the function of cardiopulmonary baroreceptors (Roddie et al., 1957; Greenfield et al., 1963; Brown et al., 1966). With the development of the LBNP chamber (Greenfield et al., 1963) the understanding of the stimulus/response characteristics of these receptors has greatly improved (Zoller et al., 1972; Wolthuis et al., 1974; Walker et al., 1979). The use of LBNP to measure cardiopulmonary baroreceptor sensitivity involves the use of two other procedures, central or peripheral venous pressure measurement and measurement of vascular resistance by venous occlusion plethysmography.

Lower Body Negative Pressure. Interest in the use of LBNP was due initially to the fact that high levels of suction produced similar responses to orthostasis (Brown et al., 1966).

Researchers later began to use mild LBNP i.e. suctions less than 20 mmHg, to simulate haemorrhage and/or reduce cardiac filling pressures (Takeshita et al., 1979; Rea et al., 1991). Rea and associates (1991) measured central venous pressure, arterial pressure and muscle sympathetic nerve activity during –5, -10 and –15 mmHg LBNP and haemorrhage of 71 $ml.min^{-1}$. They noted that central venous pressure decreased from 6.1 mmHg to 4.5, 3.4 and 2.3 mmHg with subsequent LBNP and that haemorrhage decreased venous pressure from 6.1mmHg to 3.7 mmHg over 7 min. Sympathetic nerve activity was increased by LBNP at a rate of +27% per mmHg of central venous pressure change which was comparable to the 47% increase seen after 7 min of haemorrhage. No change in mean arterial or pulse pressures occurred in either condition. Similarly no changes in mean arterial pressure at 10 mmHg LBNP (Nabel et al., 1987), –15 mmHg LBNP (Miller et al., 1991) and –20 mmHg LBNP (Norsk et al., 1993) have been observed despite significant reductions in central venous pressure. Nabel and associates (1987) during –10 mmHg LBNP did, however, record significant reductions of left atrial diameter index (1.6 to 1.4 cm/m^2 of body surface area) and left ventricular end-systolic volume index (22.8 to 19.7 ml/m^2), despite a maintenance of heart rate and stroke volume at baseline levels. These findings were supported by Norsk and colleagues (1993) who measured significant reductions in left atrial diameter of 8mm, with significantly increased noradrenaline levels suggestive of augmented sympathetic activity at 20 mmHg LBNP without alteration of mean arterial pressure. What the authors did not report, however, was the magnitude of pulse pressure change, which although observed to be not significantly different to baseline, could potentially have stimulated arterial baroreceptors.

The use of LBNP levels of between –5 and –20 mmHg, therefore, produce a reduction in cardiac filling through displacement of blood to the lower body, which is sufficient to decrease stimulation of cardiopulmonary baroreceptors in isolation from arterial receptor function, which remains unaltered due to the maintenance of mean arterial and pulse pressures at baseline levels (Zoller et al., 1972). Arterial receptors may be stimulated, however, if significant reductions in pulse pressure occur.

Central Venous Pressure Measurement. Gauer and Sieker (1956) developed a method of measuring venous pressure from an arm vein whilst the subject was in the lateral decubitus position which enabled changes in central venous pressure to be monitored. When an arm

hangs dependent beneath the body, with the subject lying horizontally on his/her side, an uninterrupted column of blood exists between the arm and right atrium throughout the cardiac cycle. Measurement of venous pressure from an antecubital vein in the dependent arm does not provide an absolute measure of central venous pressure but does provide a measure of change in central venous pressure. Due to ease of use and the low invasive nature of this technique investigators now commonly use the Gauer and Seiker method during investigations of cardiopulmonary baroreceptor function (Mack et al., 1993; Mack et al., 1987; Convertino et al., 1994).

Strain Gauge Plethysmography. A strain gauge plethysmograph incorporating a mercury in silastic rubber band was developed by Whitney as an alternative to water plethysmography for use in changing environmental temperatures (Whitney, 1953; Whitney, 1954). Plethysmography offers a useful method for estimating vascular resistance through the derivation of a measure of rate of change in volume from change in limb circumference. The change in limb circumference is brought about by venous occlusion in which a cuff is placed proximal to the section of limb to be assessed and is inflated to a pressure exceeding venous pressure thus preventing venous outflow. During forearm blood flow measurement, arterial flow to and from the hand is arrested by means of a second cuff to prevent blood flow between the forearm and the hand (Greenfield, 1960; Kerslake, 1949). Mean arterial pressure divided by blood flow provides the measure of vascular resistance. If a section of a limb such as the forearm or calf is to be assessed, the predominant site of blood flow is from skeletal muscle. The rate of change in volume of the section of limb when venous outflow is stopped is therefore essentially the blood flow to the skeletal muscle in the section of the limb.

Whitney's technique involves the placement of a strain gauge comprised of a hollow silastic rubber band filled with mercury around the widest circumference of the limb section to be measured (Whitney, 1954). Leads from two copper plugs in contact with the mercury at each end of the band form one arm of a Wheatstone bridge. If the bridge is balanced for a given degree of extension of the silastic band, subsequent changes in the length of the band alter the resistance which is recorded by a galvanometer. A linear relationship exists between change in length of the gauge and resistance thus offering a means to measure change in limb volume and therefore rate of blood flow. Multiple determinations of forearm blood

flow during repeated periods of arterial occlusion of up to 10 min, have been successfully measured using this technique (Samueloff et al., 1966b; Walker et al., 1979; Victor and Mark, 1985; Schmedtje et al., 1996).

Integrated Baroreflex Function

The cardiovascular response to a change in position or acceleration forces upon the body is a closed loop mechanism involving a variety of receptor groups and physiological systems. Although significant benefit can be derived from the study of open loop mechanisms in which individual elements are isolated from the effects of others, such conditions do not represent the natural physiological state. The measurement of the 'integrated'[6] reflex to a change in state enables the assessment of the overall response of the complete organism. One method in which the combined effect of all systems can be evaluated is by the use of Valsalva's manoeuvre.

Valsalva's Manoeuvre. Antonio Maria Valsalva (1666-1723) described a technique whereby a strenuous and prolonged expiratory effort against a closed glottis *'temporarily arrested blood flow to the heart'*. The straining involved produces an abrupt but transient rise in intra-thoracic pressure eliciting a reflex response derived from all of the major receptor groups, i.e. carotid, aortic and cardiopulmonary. Numerous investigations of the technique have established that the typical response can be divided into several descriptive phases (Hamilton et al., 1936; Stone et al., 1965).

A recognised standard protocol for the performance of the manoeuvre does not exist, however attempts at standardising certain aspects have been made. Of the variables involved pre-expiratory effort lung volume appears to be the least standardised quantitatively. The magnitude of Valsalva's manoeuvre responses differs according to the pre-expiratory effort lung volume used (Evetts and Russomano, 1995). The difficulty in measuring the lung volume used for a given expiratory effort has meant that most studies offer qualitative estimates of volume (Buda et al., 1979; Dawson et al., 1999). Brooker and co-workers (1974), Stone and colleagues (1965) and Goldstein and associates (1982) suggest that

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[6] Baroreflex derived from the responses of all baroreceptor groups.

maximal (unforced) inhalation prior to the manoeuvre offers an acceptable individual standard which can be qualified and produces acceptable responses.

Protocols using expiratory pressures of 40 mmHg appear to be the most common and offer a pressure sufficient to elicit a brisk response (Greenfield et al., 1967; Brooker et al., 1974; Dawson et al., 1999). The intensity of strain can be considered to be the product of intensity of expiratory effort over time. Maximal and near maximal responses have been recorded using pressures of 30 - 50 mmHg (Brooker et al., 1974; Korner et al., 1976; Goldstein et al., 1982). Duration of expiratory effort has varied between 7 s (Buda et al., 1979) and 30 s (Stone et al., 1965), but more commonly a 15 s expiratory effort is used (Ten Harkel et al., 1990; Schlegel et al., 1998; Dawson et al., 1999). The duration should be long enough to bring about arterial pressure lowering sufficient to produce a sympathetic constrictor response. Responses to Valsalva's manoeuvres show arterial pressure beginning to rise after approximately 10 s of expiratory effort i.e. as a result of the combination of tachycardia and vasoconstriction (Evetts and Russomano, 1995).

A refinement of the technique involves the placement of a leak in the system such that the expiratory effort cannot be maintained by the pressure in the mouth with the glottis closed (Stegemann et al., 1988; Ten Harkel et al., 1990). Investigators have used leaks in the region of 1 $mmHg.s^{-1}$ (Korner et al., 1976) to ensure that the pressure at the mouth is equivalent to that of the lungs.

The postures adopted for Valsalva's manoeuvres in previous work range from semi-recumbent (Smith et al., 1987) and supine (Korner et al., 1976; Palmero et al., 1981) to standing (Ten Harkel et al., 1990). The Primary effect of posture is upon blood re-distribution; i.e. a horizontal posture leads to a more 'square wave response'. A vertical posture may lead to earlier signs and symptoms of syncope in extreme cases due to a greater arterial pressure decrease resulting from the increased hydrostatic gradient associated with this posture.

Analysis of *Valsalva's Manoeuvre Response.* The arterial response during and after Valsalva's manoeuvre was divided by Hamilton and colleagues (1936) in to four discrete phases to aid analysis and a standardised diagnosis. The measure of baroreflex sensitivity can be obtained from the slope of the regression line derived from the systolic pressure to R-R interval relationship during phase II of the manoeuvre (Schlegel et al., 1998). The more

pronounced response of phase IV, however, usually provides a larger and more distinct change in arterial pressure for the purposes of analysis and thus is more commonly used (Palmero et al., 1981; Goldstein et al., 1982; Smith et al., 1987). Figure 2.3 illustrates a typical arterial response to a Valsalva's manoeuvre.

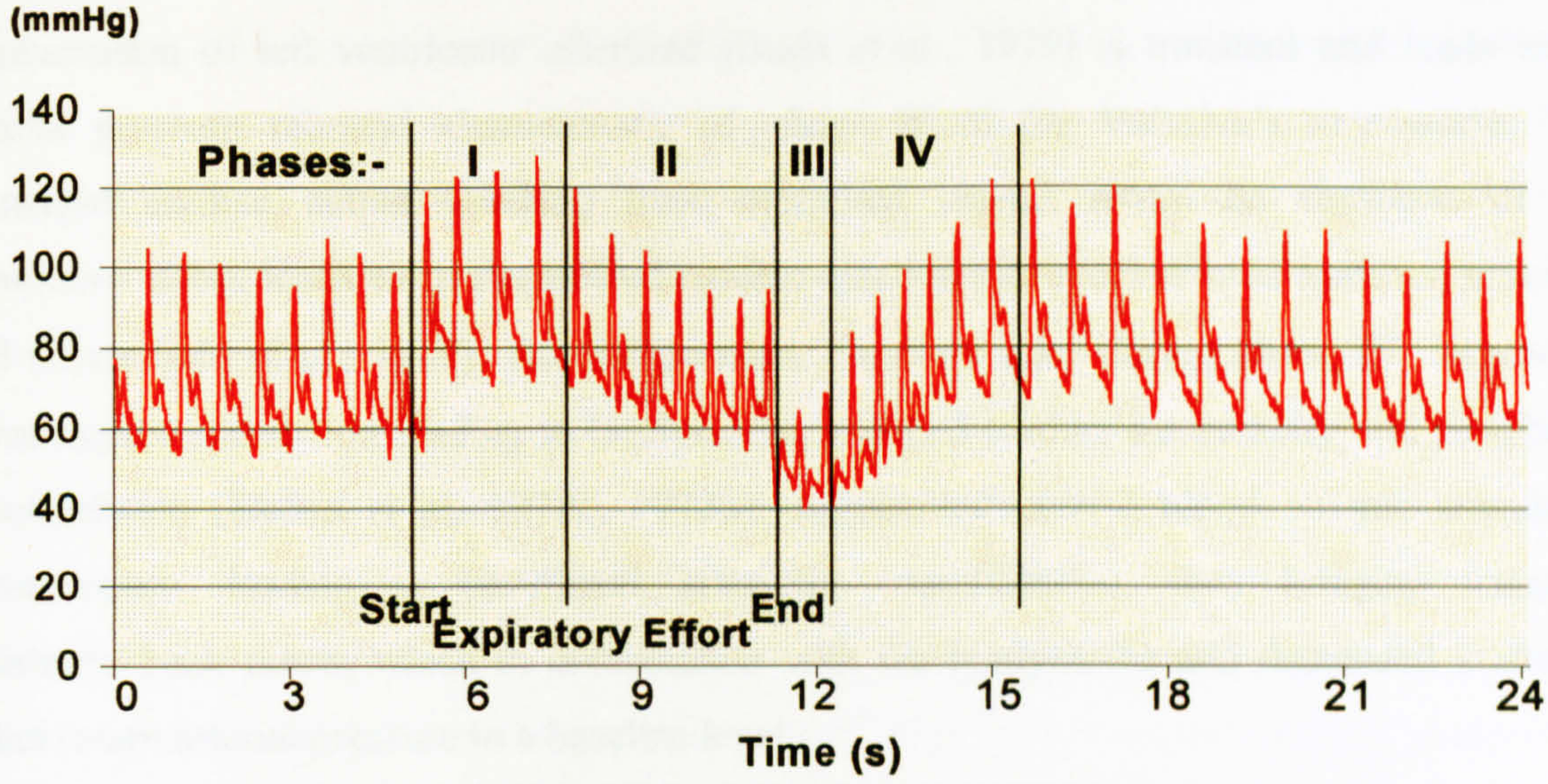

FIGURE 2.3. TYPICAL ARTERIAL PRESSURE RESPONSE TO VALSALVA'S MANOEUVRE OF 40 MMHG FOR 10 S. The response is divided in to 4 phases as described by Hamilton (1936).

Physiological Response to Valsalva's Manoeuvre. The 4 phases of the Valsalva's manoeuvre described by Hamilton and colleagues (1936), are clearly defined by marked changes in arterial pressure and heart rate. *Phase* I is recognised as the initiation of the expiratory effort leading to a rise in arterial pressure and slowing of heart rate. This transient hypertension results from increased intrathoracic and intra-abdominal pressures compressing the heart and aorta propelling blood into the peripheral vascular bed (Hamilton et al., 1936; Eckberg and Sleight, 1992). Subsequent baroreceptor stimulation then produces a reflex slowing of the heart. *Phase II* (expiratory effort) identifies a reduction in arterial pressure followed by a recovery back towards baseline levels concomitant with an accelerated heart rate. The heightened intrathoracic pressure during phase II impedes venous return to the heart therefore reducing filling pressure, cardiac volumes and cardiac output (Greenfield et al., 1967; Korner et al., 1976). Pulse pressure is reduced in all baroreceptor areas (Eckberg and Sleight, 1992) decreasing receptor stimulation and thus reducing afferent discharge. The

resulting augmentation of sympathetic efferent activity and reduced vagal efferent activity to the heart, lead to an increase in cardiac rate and contractility and peripheral arteriolar and venous tone. These produce a recovery of arterial pressure and cardiac output towards baseline levels although these are not always regained. *Phase III* is a brief reduction in arterial pressure combined with a tachycardia as a result of the fall of intrathoracic pressure on cessation of the expiratory effort. This mechanical rather than neural effect, including augmentation of left ventricular afterload (Buda et al., 1979) is transient and leads to an arterial pressure rebound characteristic of *phase IV* of the Valsalva's manoeuvre. The increased cardiac output resulting from improved venous return on cessation of the expiratory effort, leads to an augmented cardiac ejection into a constricted systemic vascular bed (Greenfield et al., 1967). Arterial pressure therefore rises during phase IV, increasing baroreceptor stimulation leading to bradycardia, reduced cardiac contractility and peripheral vasodilatation (Delius et al, 1972a, 1972b). Augmented central blood volume stimulates baroreceptors leading to peripheral arteriolar vasodilatation, thus bringing vascular resistance back down, which in combination with the bradycardia and decreased inotropic effect return arterial pressure to a baseline level.

Baroreceptor Group Interaction. Baroreflex responses to physiological perturbations such as altered arterial blood pressure and cardiac filling are derived from a complex interaction of the activity from a number of receptor groups. It is apparent that a simple summation or negation of receptor group responses cannot explain the usual integrated baroreflex. Investigations of animal baroreflexes indicate that an inhibitory interaction may exist between cardiopulmonary and arterial baroreceptors (Vatner et al., 1975; Cornish et al., 1989; Holmberg et al., 1983). Ludbrook and Graham (1984) investigated the vascular resistance and arterial pressure responses of rabbits to acute changes in blood volume. The authors found that when cardiac and arterial receptor groups were intact a 27% reduction in blood volume resulted in an increase in vascular resistance which was 60% less than the sum of their independent effects. They concluded that although both receptor groups played an important role in moderating the effects of blood volume changes, a significant negative interaction existed.

With regards to humans, Victor and Mack (1985) were able to induce a two-fold augmentation of the forearm vasoconstrictor response to neck pressure by means of non-

hypotensive LBNP. Shi and colleagues (1993a, 1993b, 1997) after a series of studies of the issue suggested that a significant degree of cardiopulmonary inhibition may only be observable during augmented cardiac filling when a threshold level is passed. The group recorded no significant change in carotid sinus receptor function after 6% dextran in saline infusion resulted in a 1.7 mmHg increase in central venous pressure, but did observe a significant inhibition of the heart rate and arterial pressure responses (by 38% and 25% respectively), as a result of a 9% expansion of blood volume (3.6 mmHg increase in central venous pressure). Their work and that of Pawelczyk and Raven (1989) show that the cardiac afferent vagal activity to the cardiovascular centre increases during cardiopulmonary receptor loading and decreases during unloading. The augmented afferent traffic appears to increase tonic inhibition of the carotid baroreflex.

Aortic and carotid receptor function have been determined independently during phenylephrine induced increases of arterial pressure combined with neck chamber pressure to counteract increased carotid sinus pressure and using LBNP to counter increased central venous pressure (Shi et al., 1993a; Convertino and Baumgartner, 1997). Shi and co-workers (1993) found that the aortic baroreceptor gain of their hypervolaemic subject group (high fitness) was significantly less than that of their normovolaemic group (moderate fitness). Furthermore the ratio of aortic to carotid gain was estimated to be 6.5:3.5 in their low fit subjects and 4:6 in their highly fit subjects. Although chronic alterations in blood volume resulting from exercise training may not be associated with the same mechanisms that exist during acute changes in volume, Convertino and Baumgartner (1997) measured significant augmentation of the aortic-cardiac baroreflex during acutely induced hypovolaemia.

Central venous pressures of between 1 and 9 mmHg have been reported not to influence cardiac rate responses to arterial baroreceptor stimulation in man (Takeshita et al., 1979). Shi and co-workers (1997), however, recorded a significant reduction in carotid baroreflex control of heart rate and mean arterial pressure during an acute increase in blood volume (+9.5%) produced by dextran/saline infusion, but pointed out that the concomitant increases in systolic and pulse pressures could have independently affected arterial baroreflex function. A comprehensive investigation of human baroreflex interaction by Pawelczyk and Raven (1989) found a clear indication of augmented carotid baroreflex control of heart rate

and blood pressure during reduced central venous pressure as derived by non-hypotensive (5 to 20 mmHg) and hypotensive (> 35 mmHg) LBNP.

It is plausible that a negative interaction between cardiopulmonary receptor function and aortic baroreceptor control of heart rate may exist in humans. A decrease in cardiopulmonary baroreceptor stimulation resulting from hypovolaemia may lead to a reduction of the inhibition of arterial receptor function and thus an augmented sinoaortic–cardiac baroreflex.

2.5 EXERCISE TRAINING AND DETRAINING

2.5.1 Categorisation of Fitness

Brief very high intensity exercise lasting less than 10 s relies almost exclusively on the adenosine triphosphate-phosphocreatine (ATP-PC) stores as the source of energy (McArdle et al., 1991; Smith and Hill, 1991). High intensity exercise that is maintained for periods of 30 to 90 s involves the primary derivation of energy from glycolysis (Medbo and Tabata, 1989). The reliance on the ATP-PC and glycolytic systems for energy production over 90 s has lead to high intensity exercise of this duration being termed 'anaerobic'. Exercise of lower intensity that can be sustained for several minutes or more is generally termed 'aerobic' as a result of the oxidative energy system being the primary energy provider (Margaria, 1963; Bhambhani and Singh, 1985).

There are, therefore, grey areas between what is termed 'anaerobic' exercise and what might be considered 'aerobic' e.g. 100 s of maximal running. With the exception of these 'grey areas' exercise can be categorised as one or the other with relative confidence that either the ATP-PC+glycolytic or the oxidative systems are the major sources of energy. For example maximal sprinting for less than 25 s can be safely termed 'anaerobic' and cycling for 25 min is certainly 'aerobic' in nature.

2.5.2 Measurement of Maximum Oxygen Uptake

Endurance performance is strongly related to the capability to take in and use oxygen (Åstrand and Åstrand, 1958; Glassford et al., 1965; Keren et al., 1980). Aerobic fitness has

therefore been assessed by means of direct $\dot{V}O_2$max measurement for a number of decades (Taylor et al., 1955). A variety of direct measurement, maximal protocols are used, all of which derive similar $\dot{V}O_2$max values (Keren et al., 1980; Montoye et al., 1986). The element of the assessment which probably produces the greatest difference between protocols is that of mode of exercise (Shepherd, 1984). Comparisons of $\dot{V}O_2$max values derived from different forms of exercise undertaken by different subject groups highlights the specificity of assessment protocols (Glassford et al., 1965; Kamon and Pandolf, 1972; McConnell, 1988). An inappropriate choice of mode of exercise may result in values ~5-10% lower than the subjects might otherwise achieve (McConnell, 1988).

Circadian changes also directly affect intrasubject $\dot{V}O_2$max variation (Shepherd, 1984). $\dot{V}O_2$max may vary by approximately 5% during the course of 24 h in the same subject (Irvin and Drummond, 1982). Changes in maximal heart rate during the course of 24 h mirrors those of $\dot{V}O_2$max (Irvin and Drummond, 1982). Consequently, intrasubject or longitudinal comparison of $\dot{V}O_2$max should ensure assessments occur at the same time of day.

With the exception of mode of exercise and circadian rhythm and providing gas and volume analysis is accurate, results vary little according to other details of the protocol e.g. length of stages, use of speed or load or both (Shepherd, 1984). The continuous, incremental protocol involving stages of between 1 and 3 min is considered the standard protocol (Saltin and Åstrand, 1967; Kamon and Pandolf, 1972; Convertino et al., 1984).

2.5.3 Principles of Training

The fundamental principles of exercise training which need to be adhered to in order to elicit physiological adaptations can be classified as 1. Overload, 2. Specificity and 3. Reversibility (McArdle et al., 1991; Skinner, 1991).

Exercise overload, that is exercise beyond an individual's normal activity range, must be applied in order to affect adaptation appropriate to a given activity (Hellebrandt and Houtz, 1956). Such an overload can be achieved by manipulating the frequency, duration and/or intensity of the exercise in order that the body is forced to work close to its maximal capabilities. The specificity principle shows that exercise leads to adaptations associated with the metabolic and physiological systems used for a specific activity and those systems not used remain predominantly unaffected (Viru and Viru, 1993; Tanaka, 1994). The

principle of reversibility is such that training induced adaptations are noticeably reduced after 2 (Houmard et al., 1992) to 8 wk (Coyle et al., 1984; Hickson et al., 1985; Coyle et al., 1986) of cessation of training. Consequently the transient, reversible nature of training induced adaptations is such that appropriate exercise training must continue if fitness is to be maintained and that to a large degree the adaptations will be lost if training is suspended for more than 4 to 8 wk.

2.5.4 Adaptations to Aerobic Training

Aerobic activity leads to increases in muscular capillarisation, mitochondria, quantity of oxidative enzymes, plasma volume and stroke volume, left ventricular dimensions and an improved ventilatory capability (Frick et al., 1970; Rowell, 1974; Viru and Viru, 1993; Branch et al., 1997). Branch and associates (1997) recorded significant increases in $\dot{V}O_2max$ (21.6%), blood volume (5%) and plasma volume (6%) as a result of 12 wk of regular cycle training for their female subjects. Similarly, significant increases in $\dot{V}O_2max$ (17.2%), blood volume (11%) and plasma volume (14%) have been reported for male subjects as a result of 8 wk of cycle training (Green et al., 1991). Cardiac mass has been found to be 19% and 18% greater following 4 and 10 wk of endurance training in rats (Hickson et al., 1983) and humans (Hickson et al., 1985) respectively. Hickson and co-workers (1985) specifically reported a significant 5% increase in left ventricular diastolic internal diameter.

Such adaptations enhance the athlete's ability to oxidise fat and carbohydrate and perfuse the muscles and essential organs with blood at a pressure and rate appropriate to the requirements of the aerobic exercise undertaken. Consequently aerobic performance improves whereas anaerobic capability is little affected.

2.5.5 Detraining Effects

Training induced physiological adaptations are lost relatively quickly when physical training is stopped. The rate of loss and the systems which are affected appear to vary according to factors such as subject training history, phenotype, genotype and form of fitness. Greenleaf and associates (1994) found that 30 d of inactivity (bed-rest) was sufficient to decrease work output (isokinetic knee extension) by 16%. Cardiac mass has been estimated to have

decreased by a significant 22% and 11% after 13 wk of detraining (Maron et al., 1993) and 15 wk of reduced training (Hickson et al., 1985) respectively. Left ventricular diastolic internal diameter, however, remained elevated despite reduced training in the subjects of Hickson and associates (1985). After a 42 d bed-rest study Ferretti and co-workers (1997) measured significant reductions in maximal cardiac output (-30.8%) and $\dot{V}O_2max$ (-16.6% i.e. 39 to 33.0 $ml.kg^{-1}min^{-1}$), and significant decreases of 16.6% and 11% in mitochondria density and oxidative enzyme activity, respectively. Training induced hypervolaemia is significantly reduced (-9%) after as little as 14 to 28 d detraining primarily as a result of decreased plasma volume (-12%) (Coyle et al., 1986). Interestingly, however, Coyle and colleagues (1986) report no significant reduction in capillarisation after detraining.

Of primary importance during detraining is the intensity element of the programme. Decreased duration and or frequency with a maintenance of intensity at the subject's usual level may not lead to significant reductions in aerobic capability over a month (Neufer, 1989). It has been clearly shown that a reduction in the intensity of the exercise undertaken is of primary importance if aerobic fitness is to be reduced and aerobic adaptations to be lost, even if all other elements are maintained at normal levels (Coyle et al., 1984; Neufer, 1989). In a detailed study of the course of fitness adaptation loss due to detraining Coyle and colleagues (1984) showed that the greatest rate of loss in fitness related variables ($\dot{V}O_2max$, maximal cardiac output, exercise stroke volume) occurs during the first 21 d, with an apparent levelling off of reductions from approximately 56 d.

2.6 FITNESS AND ORTHOSTATIC TOLERANCE

2.6.1 Head-up Tilt and Stand Tests.

Stegemann and co-workers (1974) investigated the effects of altering pressure around the area of the carotid sinus in endurance trained and untrained subjects. Their results indicate that the carotid baroreceptor sensitivity of their athletic group was significantly less than that of the control group. They concluded that the diminished baroreflex function would be advantageous during exercise, but disadvantageous during orthostasis. Although baroreflex function is not a direct measure of orthostatic tolerance the authors reported results from previous work in which they examined tilt-table responses after water immersion which

showed that 7 athletes (n = 8) and no non-athletes (n = 8) became syncopal (Stegemann et al., 1969). In neither study, however, did they quantify the fitness of their subjects.

Two investigations have estimated the $\dot{V}O_2max$ of their subjects in one case before and after a 4 month endurance training programme (Lansimies and Rauhala, 1986) and in the other according to whether the subjects became pre-syncopal during head-up tilt or not (Shvartz and Meyerstein, 1972). In both studies no relationship was found between the measure of fitness and orthostatic tolerance, however, their use of predictive tests to measure $\dot{V}O_2max$ involved a degree of error which would have been in the range of ± 15% (Keren et al., 1980; Grant et al., 1995) and judging by the mean $\dot{V}O_2max$ values (between 43 and 48 $ml.kg^{-1}min^{-1}$ for each study) all subjects were only moderately fit and thus may not have shown sufficient training adaptations to adversely affect orthostatic tolerance. Cybulski and colleagues (1999) recently measured $\dot{V}O_2max$ directly before and after a 10 wk training programme, however despite a significant increase in aerobic fitness their subjects were only able to achieve a mean value of 46.3 $ml.kg^{-1}min^{-1}$. Furthermore the investigators examined responses to 8 min of quiet standing and thus were not able to measure orthostatic tolerance per se; hence the true effect on tolerance was not studied.

Three groups of investigators have examined differences in orthostatic tolerance between groups of subjects exhibiting large differences in aerobic fitness (athletes' $\dot{V}O_2max$ > 55 $ml.kg^{-1}min^{-1}$, non-athletes' < 45 $ml.kg^{-1}min^{-1}$) in which we might expect to see significant training induced physiological adaptation in the fit subjects (Klein et al., 1969b; Williamson et al., 1992; Shvartz, 1996). Of these studies Klein and colleagues (1969b) found no effect of fitness on orthostatic tolerance, although they used suspension in a parachute harness to produce head-up tilt and may therefore have impeded blood flow to or from the lower body. Williamson and associates (1992) found that 5 out of 6 of their fit subjects (mean $\dot{V}O_2max$ 61.7 $ml.kg^{-1}min^{-1}$) and only 1 out of 6 of their controls (38.4 $ml.kg^{-1}min^{-1}$) became pre-syncopal within 30 min of 70° head-up tilt after 4 hours of head-down tilt. These results show a significant negative effect of endurance fitness, however, the authors do not provide details of the gender of their subjects. Women appear to have a poorer tolerance to orthostatic stress than men (White and Gotshall, 1995; Convertino, 1998b) and thus in a cross sectional comparison both groups require the same gender ratio if a bias is to be avoided. Shvartz (1996) observed significantly less cases of syncope in their fit group (0) than in their unfit group (8), using a 20 min stand test to examine tolerance. The

unusual aspect of their study design which may have a bearing on the results, however, is that all subjects conducted their $\dot{V}O_2max$ assessments within 10 or 15 min of their assessment of orthostatic tolerance, irrespective of whether they became pre-syncopal or syncopal. It might be conjectured that a subject who became syncopal may not achieve a true $\dot{V}O_2max$ 15 minutes later and thus the 'fainters' appear to have lower $\dot{V}O_2max$ values than they might otherwise have.

Probably the most controlled study of orthostatic tolerance using head-up tilt is that of Convertino and colleagues (1984) who used a longitudinal design to observe the effect of 8 d of cycle ergometer training on a group of 8 subjects. The subject group mean $\dot{V}O_2max$ increased from 55.3 to 60.3 $ml.kg^{-1}min^{-1}$ with corresponding to a greater mean time to pre-syncope at 60° head-up tilt from 40 to 47 min.

2.6.2 Progressive Lower Body Negative Pressure Tests

Luft and associates (1976), when investigating the effects of dehydration upon the orthostatic response, commented that their 'runners' appeared more susceptible to LBNP than their untrained subjects. Since that time a number of well controlled studies have reported what appears to be mixed findings regarding the effect of fitness or exercise training upon tolerance to progressive LBNP (Bassett-Frey et al., 1987; Smith et al., 1988b; Convertino et al., 1990b; Levine et al., 1991; Stevens et al., 1992; Savard and Stonehouse, 1995; Raven et al., 1998). Of these studies four compared minimum and maximum group mean $\dot{V}O_2max$ values of at least 42 $ml.kg^{-1}min^{-1}$ and 60 $ml.kg^{-1}min^{-1}$, all of which showed an adverse effect of high $\dot{V}O_2max$ upon tolerance (Smith et al., 1988b; Levine et al., 1991; Stevens et al., 1992; Savard and Stonehouse, 1995). Savard and co-workers (1995) examined the cardiovascular responses of intercollegiate cyclists (mean $\dot{V}O_2max$ of 72.3 $ml.kg^{-1}min^{-1}$), swimmers (mean $\dot{V}O_2max$ of 71.1 $ml.kg^{-1}min^{-1}$) and untrained controls (43.3 $ml.kg^{-1}min^{-1}$) to progressive LBNP. During LBNP 5 cyclists, 3 controls and no swimmers became pre-syncopal ($n = 8$ for each group). At the highest level of LBNP (50mmHg) similar reductions in stroke volume and cardiac output were noted for each group. Systemic vascular resistance, however, was significantly less for the cyclists.

Comparative results indicating a positive effect of the exercise trained state upon tolerance to LBNP have been reported by Convertino and colleagues (1990b) and Raven and

associates (1998). Twenty four sedentary volunteers undertook 10 wk of endurance training, elevating mean $\dot{V}O_2max$ from 40.8 to 44.1 $ml.kg^{-1}min^{-1}$ concomitant with a 9% increase in blood volume (Convertino et al., 1990b). Raven and associates (1998) detrained 19 subjects for 8 wk reducing mean $\dot{V}O_2max$ from 45.1 to 41.9 $ml.kg^{-1}min^{-1}$ and decreasing blood volume by 4.2%. Tolerance of progressive LBNP (cumulative stress index) was significantly less in the less fit state for both studies (-28% (Convertino et al., 1990b), -13% (Raven et al., 1998)).

Bassett-Frey and co-workers (1987) examined the responses of 45 subjects with a range of $\dot{V}O_2max$ values between 23 and 55 $ml.kg^{-1}min^{-1}$ to incremental LBNP to a pressure of –50mmHg. No difference was measured between the fitness levels of the subjects who became syncopal (n = 6, $\dot{V}O_2max$ = 39.2 $ml.kg^{-1}min^{-1}$) and those that did not (n = 39, $\dot{V}O_2max$ = 37.6 $ml.kg^{-1}min^{-1}$).

2.6.3 'Exercise Training – Orthostatic Tolerance' Relationship.

The work considered so far appears to indicate that highly trained subjects may show lower orthostatic tolerance than subjects or a trained condition of lesser fitness, which has lead investigators to suggest that a threshold level of fitness around 60 $ml.kg^{-1}min^{-1}$ may be required to show an effect (Raven et al., 1987; Convertino, 1993). Raven and Pawelczyk (1993) pointed out that reduced orthostatic tolerance may only be quantifiable in subjects who have trained at high intensities for many months or years, i.e. that the key may be 'training' rather than fitness per se. Levine (1993) hypothesised that both very fit and very unfit people may be adversely affected and thus the relationship may take the form shown in Fig 2.4.

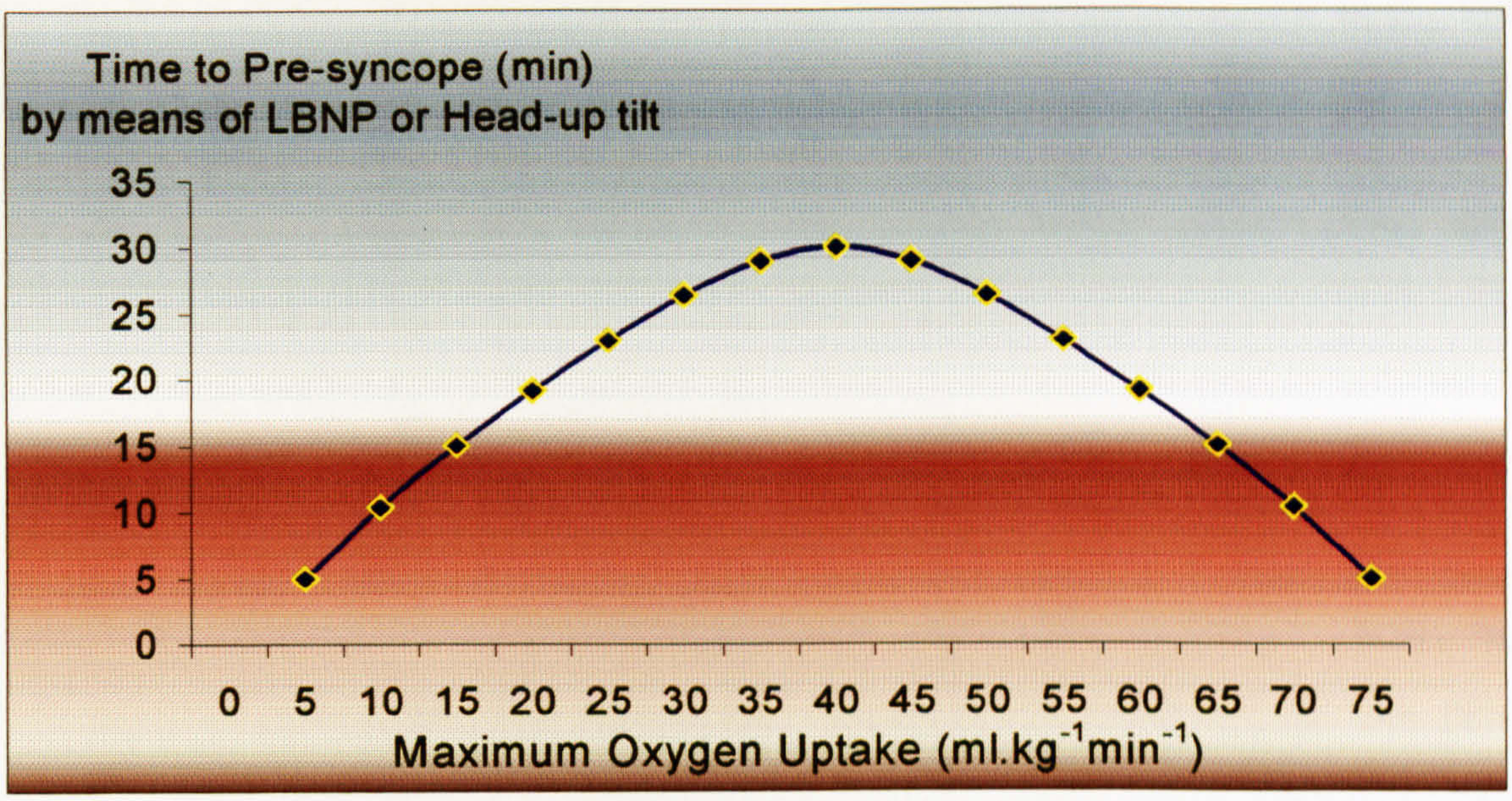

FIGURE 2.4. HYPOTHESISED MAXIMUM OXYGEN UPTAKE/ORTHOSTATIC TOLERANCE RELATIONSHIP (Levine, 1993).

The results from the LBNP studies outlined above fit Levine's model with the apparent exception of that of Bassett-Frey and colleagues (1987). The breadth of $\dot{V}O_2max$ values recorded for their subjects, however, offers the possibility that the small intolerant group may have consisted of a combination of moderately high fit subjects ($\dot{V}O_2max$ greater than 50 $ml.kg^{-1}min^{-1}$) and very unfit subjects (less than 25 $ml.kg^{-1}min^{-1}$) whose mean $\dot{V}O_2max$ may have been 39 $ml.kg^{-1}min^{-1}$ and thus not significantly different to that of the 'tolerant' group (38$ml.kg^{-1}min^{-1}$), in which case, Levine's model could describe their findings.

With regards to the head-up tilt/stand investigations, however, the relationship does not fit all cases. By excluding the studies in which fitness was estimated (Shvartz and Meyerstein, 1972; Lansimies and Rauhala, 1986) and in which design flaws may have affected results (Klein et al., 1969b; Shvartz, 1996) three head-up tilt/stand studies remain for consideration, two of which have results which do fit Levine's hypothesised relationship (Williamson et al., 1992; Cybulski et al., 1999) and one that does not (Convertino et al., 1984). Although Convertino and co-workers (1984) conducted a thorough training study the length of training (8 d) may have been insufficient to elicit the adaptations necessary to adversely affect orthostatic tolerance (Raven and Pawelczyk, 1993). Furthermore, the resistive nature of cycling may have lead to anaerobic adaptations such as increased muscle mass (McCarthy et al., 1997) or decreased vascular compliance in the thighs and calves

(Convertino et al., 1988) which could aid tolerance to head-up tilt (Greenleaf et al., 1985) and thus tolerance improved despite a change in $\dot{V}O_2max$ from 55 to >60 $ml.kg^{-1}min^{-1}$.

2.7 TRAINING INDUCED PHYSIOLOGICAL ADAPTATIONS ASSOCIATED WITH ORTHOSTATIC INTOLERANCE

2.71 Vascular Control.

Luft and associates (1976) report a significant correlation between $\dot{V}O_2max$ and vascular compliance in the leg (r = 0.72) and $\dot{V}O_2max$ and tolerance to LBNP (r = -0.75). They suggested that their runners pooled more blood in their lower extremities than non-athletes thus exacerbating the orthostatic central hypovolaemia induced by LBNP leading to reduced tolerance.

Increased vascular compliance in endurance athletes may be as a result of training induced changes in leg muscle mass (Convertino et al., 1988) reduced vasoconstrictor responsiveness (Mangseth and Bernauer, 1980) or enhanced vasodilator responsiveness (Rywik et al., 1999). Pawelczyk and Raven (1989) calculated that the increase in leg compliance associated with 8 wk of training, however, only lead to an additional 1% accommodation of fluid in the legs. Snell and colleagues (1987), however, found that their athletic subjects (mean $\dot{V}O_2max$ of $67ml.kg^{-1}min^{-1}$) had significantly greater leg vascular conductance than their control group (mean $\dot{V}O_2max$ of $47ml.kg^{-1}min^{-1}$) which appears to support the possibility of a greater effect. These authors, however, did not specifically measure orthostatic tolerance and were therefore not able to show a causal relationship. Raven and associates (1984) found no difference in leg compliance between their very fit (mean $\dot{V}O_2max$ of $70ml.kg^{-1}min^{-1}$) and average fit subjects (mean $\dot{V}O_2max$ of $41ml.kg^{-1}min^{-1}$) during LBNP, despite indications that the very fit group had less effective cardiovascular response to central hypovolaemia. Although changes in fluid capacitance of the legs might contribute slightly to orthostatic intolerance it is possible that similar mechanisms may cause larger degrees of pooling in the regions of the pelvis (Raven and Pawelczyk, 1993; White and Montgomery, 1996).

The mechanisms by which lower vasoconstrictor responsiveness might occur can be postulated to exist either pre or post vascular receptor sites. Altered basal parasympathetic

activity may be partially responsible for the augmented capability for vascular conductance (Smith et al., 1988a; Smith et al., 1988b). As a result of training induced increases in skeletal muscle capillarisation a heightened baseline vagal activity may be a necessary to provide an appropriate level of peripheral vascular resistance for the correct maintenance of arterial pressure during exercise. Alternatively, a change in state of vascular smooth muscle responsiveness has been proposed by a number of investigators (Mangseth and Bernauer, 1980; Raven et al., 1984; Smith et al., 1988b). How and where such a change in state occurs is not clear, but a reduced sensitivity of α-adrenergic receptors (Pavlik and Frenkl, 1975) or augmentation of β-adrenergic receptor sensitivity has been proposed (Williams, 1985).

2.7.2 Augmented Parasympathetic baseline.

Endurance training alters physiological function in order that a greater fraction of skeletal muscle conductance can be utilised without necessitating additional vasoconstrictor tone to maintain blood pressure (Neufer, 1989; Levine, 1993). This appears to be mainly as a result of increased vagal activity, and possibly as a partial reduction in sympathetic activity, leading to the characteristic athletic bradycardia (Convertino, 1985). Smith and colleagues (1988a, 1988b) found that highly fit (mean $\dot{V}O_2max$ = 65ml.kg^{-1}min^{-1}) and unfit ($\dot{V}O_2max$ = 42ml.kg^{-1}min^{-1}) subjects showed the same cardiovascular responses to LBNP after parasympathetic blockade, whereas in an unblocked condition the highly trained subjects experienced significantly greater falls in systolic and mean arterial pressure than the unfit subjects, supporting the contention that a greater parasympathetic baseline exists in the trained state.

2.7.3 Training Induced Hypervolaemia.

Increased blood volume, primarily through elevated plasma volume, is associated with endurance training (Convertino et al., 1990b; Green et al., 1991) and has been found to contribute to athletic performance (Hagberg et al., 1998). Gillen and associates (1994) observed that as little as eight 4 min periods of moderately high intensity exercise increased blood volume by 3.9% 44 hours post exercise. Training induced hypervolaemia of up to +25% has been reported (Fellmann, 1992). Blood volume may decrease by 9-12% after 14 d of detraining (Coyle et al., 1986; Schmedtje et al., 1996), and plasma volume by 18.5% after

15 d of deconditioning (Crandall et al., 1994). The relationship between endurance training and hypervolaemia may be associated with reduced orthostatic tolerance, a contention supported by linear relationships noted between training induced hypervolaemia and orthostatic tolerance (Ludwig and Convertino, 1994; Jacob et al., 1998a) and changes in baroreflex function (Levine et al., 1991; Mack et al., 1991).

Shi and colleagues (1992) point out that endurance trained athletes may have up to 800ml of blood more than their untrained counterparts and that the additional volume must reside in the low-pressure side of the circulatory system. Convertino and co-workers (1984, 1990b) have reported increased blood volume as a result of exercise training, which was associated with improved tolerance to LBNP. The changes in aerobic capability, however, were either small (+8%) concomitant with a 12% increase in plasma volume (Convertino et al., 1984), or resulted in a trained value less than 50 $ml.kg^{-1}min^{-1}$ in combination with a blood volume augmentation of 9% (Convertino et al., 1990b). The lack of change in vascular conductance and associated elevated central venous pressure as a result of training, lead Convertino and co-workers (1990b) to suggest that small increases of blood volume (in the region of 10% or 500ml) might aid orthostatic tolerance by augmenting cardiac filling. They go on to hypothesise that greater increases in training induced hypervolaemia (15% or 750ml+) may be associated with vascular structure or function adaptations which could adversely affect tolerance. This would suggest that training induced hypervolaemia acts positively to aid the athlete during orthostasis, but may be insufficient to offset the adverse effects of other chronic adaptations which act to reduce tolerance in the highly fit state.

2.7.4 Cardiac Adaptations.

Training induced increase in heart size, particularly left ventricular mass, is primarily due to the effects of training induced bradycardia and an increase in sarcomere numbers (Buttrick and Scheuer, 1987). Mean left ventricular end-diastolic diameter for untrained men has been reported to be approximately 46mm whereas an endurance athlete may have a diameter of 55mm (Franklin et al., 1997). Cardiac output at rest is unchanged in endurance athletes whereas maximal cardiac output may be increase by 100% (to ~35 $l.min^{-1}$ (Franklin et al., 1997)). A reduction in resting heart rate concomitant with no change in cardiac output illustrates the augmented stroke volume associated with endurance training (Snell et al.,

1987; Convertino et al., 1990b). A highly trained endurance athlete may have stroke volumes of 136ml at rest and 184ml during maximal exercise (Franklin et al., 1997). As with small increases in blood volume it would appear that an increase in stroke volume combined with a greater range of heart rate offers a greater reserve of cardiac output and thus a positive adaptation to LBNP. Convertino and colleagues (1990) found that their moderately trained athletes were able to maintain cardiac output at lower heart rates by means of increased stroke volume at each level of LBNP thus enabling them to continue longer under the influence of LBNP before cardiac output was significantly effected. Raven and co-workers (1984) report similar findings in their very fit subjects during LBNP in that they had a significantly greater cardiac output at all levels of LBNP (up to –50 mmHg) than those of an average fit subject group. Calculated peripheral vascular resistance, however, was lower in the very fit group, combined with a marked decrease in systolic pressure for a given change in LBNP despite the augmented cardiac reserve. The authors concluded that the very fit subjects may have had a diminished ability to vasoconstrict, which could not be compensated sufficiently by their chronotropic reserve.

Smith and colleagues (1988b) studied the response to LBNP in trained (mean $\dot{V}O_2max$ = 65ml.kg^{-1}min^{-1}) and untrained (mean $\dot{V}O_2max$ = 42ml.kg^{-1}min^{-1}) subjects with parasympathetic blockade (atropine sulphate), sympathetic blockade (metoprolol tartrate) and combined blockade (atropine sulphate and metoprolol tartrate). During the fully blocked and atropine blocked conditions blood pressure was maintained equally in both groups at rest, at –16 mmHg and –40 mmHg LBNP, primarily by augmented vasoconstriction. During the unblocked and metoprolol blocked conditions the athletes experienced significantly greater falls in systolic and mean arterial pressure during LBNP. The authors suggested that elevated baseline parasympathetic activity in the trained subjects restricted reflex cardiac responsiveness which combined with an attenuated vasoconstrictor response, produces inadequate blood pressure control during hypotensive stress. The degree of endurance training required to elevate $\dot{V}O_2max$ to values in excess of 60 ml.kg^{-1}min^{-1} suggests that the high fit subjects of Smith and associates would have elicited near maximal endurance training adaptations such as heightened parasympathetic baseline activity. Such levels of adaptation may have been sufficient to have been instrumental in the reduced cardiovascular response to LBNP observed, whereas in studies in which subjects of lesser $\dot{V}O_2max$ values

are assessed, adaptations may have only been moderate and therefore did not significantly affect tolerance.

Training induced left ventricular hypertrophy may alter the structure and function of the heart (Levine, 1993; Raven et al., 1998). Several authors have implied that altered cardiac pressure/volume relationships in athletes may be associated with orthostatic tolerance. Levine (1993) after a comprehensive investigation of the structure and function of the heart after endurance training hypothesised that endurance trained individuals may have an increased capacity to utilise the Frank-Starling mechanism to aid cardiac filling during exercise. Levine observed an increase in left ventricular compliance in the trained state sufficient for a two-fold augmentation of change in stroke volume for a given change in cardiac filling pressure. Although this capability can be considered beneficial during intense exercise during orthostasis it is likely to result in an excessive fall in stroke volume when cardiac filling decreases.

Estimations of aortic and cardiac compliance suggest that endurance training results in an increase in cardiac and arterial compliance (Levine, 1993; Shi et al., 1993a). 'Remodeling' of the cardiac and arterial tissue may enable the cardiac chambers and aortic walls to expand more easily thus accommodating the training induced expansion of blood volume and cardiac output (Raven et al., 1998). In addition to potentially altering the pressure/volume relationship of the heart, increased compliance may reduce the visco-elastic coupling of the baroreceptors of the heart and aorta. The resultant increase in elasticity may require greater changes in vascular and myocardial stretch for receptor activation than would be necessary in the untrained state. Such a mechanism could explain the reduced cardiopulmonary and aortic baroreceptor sensitivities generally observed in endurance athletes.

2.7.5 Autonomic and Endocrine Systems.

High levels of aerobic training are associated with elevated parasympathetic activity at rest (Sanders and Williams, 1985; Smith et al., 1988b). The increased baseline vagal activity results in a slower cardiac rate at rest (Sanders and Williams, 1985; Convertino, 1993) and may attenuate the cardiovascular responses to LBNP i.e. inadequate vasoconstriction and

tachycardia (Smith et al., 1988a, 1988b). Raven and Pawelczyk (1993) point out that studies of the effects of training upon autonomic function in animals have shown increased vagal inhibition of sympathetic function with training. The consequence of such inhibition would be to dampen the sympathetic vasoconstriction and tachycardia response. Twelve weeks of aerobic training, however, produced no change in muscle sympathetic nerve activity at rest (Sheldahl et al., 1994) and no significant change in plasma AVP or PRA during head-up tilt was observed after 6 months of aerobic exercise training by Greenleaf and associates (1988). In the former study, however, $\dot{V}O_2max$ was elevated from 30 to only 35 $ml.kg^{-1}min^{-1}$ and in the latter from 39 to 48 $ml.kg^{-1}min^{-1}$ with no change in tolerance to head-up tilt. It is likely that for studies such as these in which the improvement in aerobic conditioning is small, training induced physiological adaptations which might affect orthostatic tolerance may not be evident. Lijnen and colleagues (1986) found that their test group of competitive runners ($\dot{V}O_2max$ not reported) had 52% lower resting PRA levels ($p < 0.01$) than their untrained counterparts. In this instance the difference in trained states may have been sufficient to enable a physiological effect to be detected.

One of the primary mechanisms for an increase in systemic peripheral resistance during orthostasis may be angiotensine-mediated vasoconstriction via sympathetic stimulation of renin release by the kidney. Convertino (1987) suggests that a shift from sympathetic to parasympathetic dominated activity, as seen in chronic endurance training, may lead to reduced PRA and thus less tolerance to orthostasis. Significantly lower resting and orthostatic stress levels of PRA in patients with clinical orthostatic intolerance have been reported in the literature (Jacob et al., 1997; Streeten, 1999). Reduced PRA with high fitness (Lijnen et al., 1986) and increased PRA associated with deconditioning (Schmedtje et al., 1996) may indicate a negative relationship between the rennin-angiotensin system response to hypotension and endurance fitness and therefore a potential mechanism for exercise training induced orthostatic intolerance.

Fritsch-Yelle and colleagues (1996) after an assessment of post mission orthostatic tolerance of 40 astronauts found that those who were unable to tolerate 10 min of passive standing post mission ($n = 8$) had significantly lower systolic and diastolic pressures and peripheral vascular resistances at rest pre-mission. Additionally, during orthostasis the intolerant subjects showed significantly smaller rises in noradrenaline than tolerant subjects. The

authors proposed that a 'hypo-adrenergic' response such as this may be partially derived from changes in central modulation of baroreceptor afferent activity. The implications of their findings are that some astronauts may be pre-disposed towards post-mission orthostatic intolerance resulting from microgravity exposure or deconditioning. Lower resting arterial pressures and vascular resistance for the intolerant astronauts may indicate low levels of sympathetic tone which, if derived from higher basal parasympathetic tone than that of their tolerant colleagues, is suggestive of a mechanism similar to that described by Convertino (1987). In this particular study fitness was not assessed, however, mean pre-mission resting (supine) heart rate for the tolerant and intolerant subjects do not indicate high levels of aerobic fitness (62 and 72 bpm respectively).

Recent research indicates that although the cardiopulmonary barorceptors contribute to the activation of the rennin-angiotensin system during orthostasis, arterial baroreceptors may play the more dominant role (Jacobsen et al., 1993; Norsk et al., 1993). Reductions in pulse pressure without alterations of mean arterial pressure, result in significant increases in PRA and AVP concentration, whereas reduced central venous pressure with unchanged pulse and mean arterial pressures may not (Norsk et al., 1993). Williamson and co-workers (1993) in an investigation of endocrine responses to head-up tilt in endurance athletes (n = 6, mean $\dot{V}O_2$max of 61.7 $ml.kg^{-1}min^{-1}$) and untrained controls (n = 6, mean $\dot{V}O_2$max 38.4 $ml.kg^{-1}min^{-1}$) found that after 4 h of head-down tilt only 1 athlete and 5 controls were able to tolerate 30 min head-up tilt. Of note was the fact that the athletes failed to increase plasma AVP concentration during orthostasis as effectively as the untrained subjects ($p < 0.01$). This appears to indicate maintenance of arterial pressure by the athletes during orthostasis, however, orthostatic intolerance is associated with falling arterial pressures prior to syncope. It could be postulated, therefore, that aerobic fitness may lead to a dissociation between arterial pressure stimulation of the baroreceptors and efferent sympathetic control of vascular tone by means of plasma renin and AVP.

2.7.6 Baroreflex System.

Arterial Baroreflex. Stegemann et al (1974) reported that the changes in heart rate and mean arterial pressure in response to neck pressure or suction were significantly less in athletes than untrained subjects (values not reported). Tipton and associates (1982) lend support to this finding because their trained rats exhibited significantly greater and faster falls in arterial pressure during LBNP, than untrained controls, a difference which was abolished after baroreceptor denervation. Smith and colleagues (1988b) used phenylephrine to induce hypertension in endurance fit, weight trained and untrained subjects. Arterial baroreflex gain was observed to be significantly less in the endurance trained group than in the untrained. Of note was the fact that the weight-trained subjects had slightly more sensitive responses than the untrained. Smith and colleagues (1988a) using LBNP to 50 mmHg, found a significantly attenuated chronotropic response during hypotension in the endurance group (-0.57 vs. –0.91 $bpm.mmHg^{-1}$ for untrained controls), thus lending support to the results of Stegemann and co-workers (1974).

Barney and associates (1988) report greater heart rate slowing for a given change in carotid sinus distension (i.e. greater baroreflex sensitivity) in their highly trained subjects (change in R-R interval of 4.00 $ms.mmHg^{-1}$) than for normal fit subjects (2.53 $ms.mmHg^{-1}$). The lack of change in tolerance to LBNP lead them to conclude that training induced alterations in arterial baroreceptor function did not contribute to orthostatic intolerance. An important difference between the protocols of Smith and colleagues (1988a) and Barney and colleagues (1988) was that in the former measurements were made several minutes after neck suction was applied, whereas the latter measured variables immediately after the application of the stimulus. Smith and co-workers (1988a) point out that the initial baroreflex-mediated chronotropic response appears to be parasympathetic based, whereas if blood pressure perturbation is prolonged beyond 30 s, the reflex becomes predominantly sympathetically mediated. Furthermore, the adaptation characteristic of baroreceptors is such that afferent activity after several minutes of stimulus action will have substantially reduced (Bronk and Stella, 1932) and thus the afferent activity profiles of the two methods would have been very different. Consequently, the timing of the baroreflex assessment is important and may explain the different findings between the two studies.

Convertino and associates (1989) measured carotid sinus reflex responses before and after 30 d of deconditioning (head-down tilt) noting a reduction in sensitivity during and after the deconditioning period (mean of 3.55 ms.mmHg^{-1} reduced to 2.45 ms.mmHg^{-1}). Similarly, carotid baroreflex sensitivity significantly decreased (4.0 ms.mmHg^{-1} to 2.8 ms.mmHg^{-1}) after 14 d of detraining (Convertino and Fritsch, 1992). After 8 wk of detraining, during which $\dot{V}O_2$max and plasma volume were significantly reduced by 7% ($\dot{V}O_2$max from 45 to 42 ml.kg^{-1}min^{-1}) and 3% respectively, Raven and colleagues (1998) observed little change in carotid baroreceptor function (approximately 2.9 to 2.8 ms.mmHg^{-1}). They did, however, find that aortic sensitivity significantly increased (-0.61 to –0.84 bpm.mmHg^{-1}). In agreement are the findings of Levine and co-workers (1991) who saw no alteration in baroreflex responsiveness in athletes compared to non-athletes using neck suction, although a fitness related upward shift in the baroreflex slope baseline was found. A few years earlier, however, Raven and co-workers (1984) found that a group of aerobically trained subjects had an increase in heart rate as a result of exposure to 50 mmHg LBNP which was significantly less than that of average fit subjects suggesting the possibility of reduced arterial baroreflex sensitivity. In support of this finding is that of Shi and colleagues (1993a) whose measures of aortic and carotid baroreflex gain indicated that the overall arterial baroreflex gain (aortic + carotid) of highly fit subjects ($\dot{V}O_2$max of 62 ml.kg^{-1}min^{-1}) was 65% less than that of low fit subjects (43 ml.kg^{-1}min^{-1}).

Cardiopulmonary Baroreflex. Greater increases in forearm vascular resistance during LBNP have been reported in student American football players (Takeshita et al., 1986). Although the fitness of the athletic group would certainly have been greater than the control group aerobic capacity was not quantified for either

In addition to examining arterial baroreflex function Raven and associates (1998) also studied cardiopulmonary function after detraining finding that mean sensitivity increased from –2.75 to –4.94 U.mmHg^{-1}. These data support earlier findings by Mack and colleagues (1987, 1991) who provided convincing evidence that the cardiopulmonary baroreflex may be attenuated in endurance trained subjects (mean $\dot{V}O_2$max values of 57 ml.kg^{-1}min^{-1} compared to 39 ml.kg^{-1}min^{-1}) and by endurance training per se (mean $\dot{V}O_2$max values changed from 37 ml.kg^{-1}min^{-1} to 45 ml.kg^{-1}min^{-1}). They used mild LBNP to examine the effect of acute reduction of central blood volume upon forearm blood flow in the trained

and untrained state. Linear relationships were noted between training induced blood volume changes and a significant reduction in baroreflex gain for both studies, -5.96 $U.mmHg^{-1}$ reduced to –4.06 $U.mmHg^{-1}$ (Mack et al., 1991) and -2.42 $U.mmHg^{-1}$ compared to -5.15 $U.mmHg^{-1}$ (Mack et al., 1993). In the longitudinal study resting forearm vascular resistance was not affected by training, however, central venous pressure rose from 9.5 mmHg to 11.3 mmHg as a result of training, producing a significant inverse relationship between the reduction in baroreflex gain and increase in blood volume (Mack et al., 1991). Convertino and associates (1990) elicited similar training induced increases in fitness over 10 wk (41 $ml.kg^{-1}min^{-1}$ to 44 $ml.kg^{-1}min^{-1}$) and also observed a significantly reduced cardiopulmonary baroreflex post training.

2.8 PHYSIOLOGICAL RESPONSE TO MICROGRAVITY.

2.8.1 Overview.

Although a number of factors affect the human body during space flight, microgravity is the principle factor of concern. The major effect of the loss of '1G' is the abolition of the hydrostatic gradient through the body and fluids normally located in the lower body move towards the upper body. This cephalic shift on entering microgravity may be as much as one to two litres (Leach et al., 1996). Increased stimulation of cardiovascular receptor groups in the upper body results in reduced sympathetic activity, PRA and atrial natriuretic peptide levels subsequent to a diuresis and hypovolaemia (Newberg, 1994). Little direct data has been produced to show a diuresis per se, however, a decrease in body fluid levels and electrolyte balance has been measured during and post flight (Leach, 1983; Sulzman, 1996).

The cephalic movement of body fluids increases cardiac pre-load due to an augmented venous return, however, unlike the effect of ground based simulations, central venous pressure in microgravity does not increase, but decreases (Buckey et al., 1996a; Foldager et al., 1996). The initial effect of microgravity on heart rate is unclear due to the confounding variables associated with space and parabolic flight. Relative to the upright position, heart rate has been observed to remain unchanged (Pump et al., 1999) or decrease (Prisk et al., 1993) on exposure to microgravity. Stroke volume has been found to be 41% elevated within the first few hours of exposure to microgravity (Prisk et al., 1993), but return towards baseline levels over subsequent days, although remaining higher than pre-flight values (Vorobyov et al., 1983; Prisk et al., 1993). Cardiac output is therefore greater in microgravity, remaining 11 to 17% higher than pre-flight (Vorobyov et al., 1983; Prisk et al., 1993).

Exposure to a microgravity environment will lead to general deconditioning of the human body such that body mass reduces (Berry, 1970), skeletal muscles atrophy (in particular the anti-gravity muscles) (Vorobyov et al., 1983; Riley, 1996) and declines in bone density (Vorobyov et al., 1983), maximum oxygen uptake (Berry, 1970) and muscular strength (Thornton and Rummel, 1977) become apparent after as little as a week (Nicogossian, 1989). The effect of the deconditioned state is not problematic for the astronaut until acceleration forces act upon the body again, upon which reduced aerobic

capability, decreased strength and a loss of tolerance to orthostasis combine to make him/her physically less effective than before the flight. The incidence of orthostatic intolerance varies according to duration in the microgravity environment and the effectiveness of any countermeasures used, but may be as high as 64% for short missions (Buckey et al., 1996b) or >90% for long stays in orbit (Vorobyov et al., 1983).

2.8.2 Microgravity Simulation - Head-down Tilt.

Head-down tilt was first used by Soviet investigators to reproduce some of the physiological effects of microgravity. Angles between 2° and 20° were initially employed, the most common of which was probably 5° C (Hyatt and West, 1976; Volicier et al., 1976; Nixon et al., 1979). An examination of the effects of various tilt angles by Kakurin and colleagues, however, indicated that the change in heart rate produced by microgravity was less than that produced by 8° head-down tilt and greater than that observed as a result of 4° (Kakurin et al., 1976). Consequently, the intermediate angle of 6° became the angle of choice (Blamick et al., 1988; Greenleaf et al., 1998; Pannier et al., 1998).

Head-down tilt causes a relocation of approximately 0.5 to 1 litre of blood from the lower to upper body during the course of 30 min (Nixon et al., 1979; Greenleaf, 1984). Tomaselli and colleagues (1987) reported that thoracic fluid volume was significantly increased after as little as 10 min of 6° head-down tilt. The cephalic shift in fluid stimulates the baro- and neurohumoral reflexes resulting in a period of natriuresis and diuresis which can result in a 9% reduction of plasma volume after 6 hr (Maillet et al, 1994) and 15% after 30 d (Convertino et al, 1990a).

Noradrenaline concentrations have been reported to decrease by 40% over 2 d of head-down tilt (Maillet et al, 1994), but be unchanged after 14 d (Schmedtje et al., 1996). The same authors report significant increases in PRA of 60% (Maillet et al, 1994) and 86% (Schmedtje et al, 1996) during the course of head-down tilt of 2 and 14 d respectively.

Mean arterial pressure has been observed to significantly rise after 1 hr (Tomaselli et al., 1987), and yet be equivalent to baseline levels after 4 hr of head-down tilt (Raimondi et al., 1998). Raimondi and colleagues (1998) found that calf and forearm blood flows significantly reduced after 4 hr of tilt indicating augmented vascular resistance. Over 10 d of head-down tilt, however, Blamick and co-workers (1988) report that arterial pulse volume

(an index of peripheral vasoconstriction) was unchanged and that therefore control of peripheral resistance was unaffected. Maillet and associates (1994) report that atrial natriuretic peptide concentration increased for 4 hr to 50% above baseline levels, but returned to pre-tilt levels thereafter. It appears, therefore, that the human physiological state during the first few hours of head-down tilt is different to that observed after a number of days.

2.8.3 Head-down Tilt and Orthostatic Tolerance

Incidence of between 17% and 50% orthostatic intolerance after 10 to 30 d of 6° head-down tilt have been reported (Blamick et al., 1988; Convertino et al., 1990a; Arbeille et al., 1995; Engelke et al., 1996). Engelke and co-workers (1996) found that 16 d of 6° head-down tilt resulted in a significant reduction in average LBNP tolerance time, significantly reduced leg vascular resistance responses, increases in heart rate, higher concentrations of PRA and lower concentrations of atrial natriuretic peptide at the point of pre-syncope than noted before head-down tilt. Similarly Arbeille and co-workers (1995) found that 28 d of head-down tilt produced significantly lower femoral artery vascular resistance responses to LBNP than pre tilt measures and that 50% of subjects became pre-syncopal during head-up tilt. A similar trend (albeit not significant) was also observed by these investigators for a cosmonaut during 14 d in orbit.

The 40% incidence of orthostatic intolerance after 30 d of head-down tilt reported by Convertino and associates (1990) was found to be related to carotid baroreflex function. Carotid baroreflex sensitivity decreased during the course of head-down tilt, but significantly more so for those subjects who subsequently became pre-syncopal during standing. Carotid baroreflex function was not related to the 15% drop in plasma volume produced by head-down tilt.

2.8.4 Microgravity and Orthostatic Tolerance

The aetiology of microgravity induced orthostatic intolerance is not clear, however, the principle factors which may be involved are the cephalic movement of body fluids (Shashkov and Aiu, 1998), changes in leg vascular diameter control (Buckey et al., 1996b), alterations in baroreflex function (Fritsch-Yelle et al., 1994), decreased exercise tolerance

and fitness (Baldwin et al., 1996), hypovolaemia (Jacob et al., 1998a) and altered sensitivity of ß-adrenergic receptors in the periphery (Tyberg and Hamilton, 1996).

Hoffler, Wolthuis and Johnson (1974) during cardiovascular examinations of the Apollo astronauts found decreases in systolic pressure, a reduction in pulse pressure and higher heart rates during LBNP after flight than those measured pre mission. Vorobyov and associates (1983) in a review of the medical results of the Salyut-6 space missions stated that intolerance to orthostatic stress was found consistently in cosmonauts whilst in space and on their return. The durations of the missions covered varied from 75 to 140 d, although the length of time in space did not correlate with the resulting degree of orthostatic intolerance. Vorobyov and colleagues (1983) point out that the mission tasks, personal exercise routines, and rehydration measures prior to a return to earth, confounded their analysis. Sandler and Convertino (1985) however, in their review of the effects of space travel using both Soviet and NASA data, concluded that similar alterations in blood pressure and heart rate responses occur during the orthostatic stress produced by standing, LBNP or head-up tilt, regardless of mission length (between 7 and 180 d). Furthermore, orthostatic tolerance has been found to be adversely affected in missions as short as 4-5 d (Fritsch et al., 1992).

Tolerance to 10 min standing was assessed in 14 astronauts before and after 9 to 14 d space flight (Buckey et al., 1996b). A significant 64% (n = 9) of the astronauts were unable to complete the task post mission. Changes in post-flight heart rates, stroke volumes and cardiac outputs induced by standing were not significantly different between tolerant and intolerant subjects. Buckey and co-workers did, however, note significantly greater post-flight vasoconstrictor responses in the tolerant group

Fritsch-Yelle and colleagues (1996) during a thorough examination of pre and post-mission orthostatic tolerance of 29 astronauts who had been in orbit for 8 to 16 d, found that 8 could not complete the post mission 10 min stand test and that post-flight intolerance was experienced to some degree by virtually all astronauts. The differences between the 'fainters' and 'non-fainters' were that the intolerant group had significantly lower peripheral resistances, attenuated plasma noradrenaline increases and greater decreases in systolic and diastolic arterial pressure during post-flight standing. Furthermore pre-flight supine and standing vascular resistance, systolic and diastolic pressures were significantly less in the intolerant group. The investigators suggest that inadequate catecholamine responses to orthostasis may be a contributing factor to the orthostatic intolerance observed.

2.8.5 Microgravity, Head-down Tilt and Baroreflex Function.

Convertino and co-workers (1989) using the Eckberg/Sprenkle technique for carotid sinus stimulation found significantly reduced baroreflex responses to ramped neck pressure-suction sequences after 30 d head-down tilt. When subjects were divided according to tolerance to a 10 min stand test after bed-rest, the intolerant subjects showed a significantly greater reduction in carotid baroreflex gain than the tolerant subjects (4.0 to 2.2 ms.mmHg^{-1} and 3.1 to 2.7 ms.mmHg^{-1} respectively). The observance of a shift in the R – R interval/stimulation pressure relationship down the R-R axis without a shift along the pressure axis provoked the authors to suggest that a resetting of the carotid baroreflex might have occurred in order to preserve resting arterial pressures throughout the deconditioning period (Convertino et al., 1989).

The data of Eckberg and Fritsch (1992) and Engelke et al (1996) support the findings of Convertino in that carotid baroreflex sensitivity was significantly reduced from 4.5 to 3.6 ms.mmHg^{-1} after only 10 d head-down tilt (Eckberg and Fritsch, 1992) and from 2.8 to 2.0 ms.mmHg^{-1} after 16 d head-down tilt (Engelke et al., 1996).

Hughson and co-workers (1994) examined spontaneous arterial baroreflex slopes[7] before, during and after 28 d of head-down bed-rest with and without 'exercise+LBNP' as a countermeasure. No difference was seen between the reflex responses of the control group and a countermeasures group, however, as with Convertino and Eckberg significant decreases in baroreflex slopes resulted from the bed-rest for the control (18.5 to 14.1 ms.mmHg^{-1}) and countermeasure (14.9 to 9.8 ms.mmHg^{-1}) groups (Hughson et al., 1994). Hughson and co-workers (1994) supported their results by measuring the spontaneous baroreflex gain of one astronaut at rest pre-mission and during space flight. The gain decreased from 17.7 ms.mmHg^{-1} pre-flight to 10.0 ms.mmHg^{-1} in flight. Unlike the head-down tilt subjects the reduction occurred without a change in baseline R-R interval, but with a slight rise in systolic arterial pressure.

More recently, comprehensive investigations into the effect of space flight have shown that microgravity appears to affect the carotid baroreflex in a similar manner to that of head-down tilt (Fritsch et al., 1992; Fritsch-Yelle et al., 1994). Fritsch and colleagues

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[7] R-R interval/systolic pressure relationships during naturally occurring increases in arterial pressure.

(1992) studied carotid baroreceptor/cardiac reflexes, provoked by neck pressure changes in the supine position before and after 4 to 5 d in orbit. From the second day after landing baroreflex slopes and ranges were seen to be significantly less in 50% of the subjects than pre-flight values. A lowering in operational point[8] was seen on the landing day in 86% of the astronauts, returning to pre-flight levels from the next day. Fritsch and colleagues (1992) point out that all subjects followed some form of fluid loading protocol before landing, these consisting of salt, salty food, water and/or juice. Plasma volume and hydration levels were not measured however, and thus it is difficult to account for the degree of effect of fluid loading on orthostatic stress.

Fritsch-Yelle and co-workers (1994) repeated the 1992 study with catecholamine assays and Valsalva's manoeuvres to assess autonomic function. Similar reductions in baroreflex slopes were seen post flight. Both noradrenaline and adrenaline levels were significantly increased for 3 d after landing. Greater changes in the magnitude of blood pressure response were seen in each stage of Valsalva's manoeuvre. R-to-R intervals were also significantly reduced for these tests, indicating a possible decrease in vagal efferent responsiveness. The authors suggest that the indications were that reductions in parasympathetic and increases in sympathetic influences on arterial pressure control were seen after space flight. They do, however, admit that again the lack of knowledge concerning the astronauts' hydration levels may have confounded the interpretation of the responses to Valsalva's manoeuvre.

Little work has been done on the effects of microgravity or simulated microgravity on the cardiopulmonary baroreflex, however, Convertino and associates (1994) conducted a 7 d head-down tilt study in which they ascertained cardiopulmonary baroreflex function by means of LBNP, forearm plethysmography and peripheral venous pressure measurement. Their results revealed an augmented post head-down tilt reflex gain which was related to reduced blood volume (-1.61 $U.mmHg^{-1}$ pre tilt, -3.2 $U.mmHg^{-1}$ post).

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[8] A measure of relative reflex buffering capacity for change in pressure above and below rest levels

2.9 SUMMARY

The inability of investigators to agree upon the nature of the relationship between orthostatic tolerance and fitness despite the existence of numerous studies examining the issue, may derive from the multitude of different subject groups used, experimental designs and modes of assessments adopted and differing concepts of orthostatic tolerance. Possibly the two principles factors which have hindered attempts to understand the issue in the past are the consideration of research results comprising data derived from the use of different methods of assessing orthostatic tolerance (i.e. LBNP and stand/head-up tilt) and the possibility that the relationship between orthostatic tolerance and aerobic fitness may not be linear.

An examination of well-controlled data with the above points in mind appears to indicate that a parabolic relationship may be evident, as hypothesised by Levine in 1993. This relationship requires that the physiological and structural adaptations associated with a change in fitness from the low state to the moderate must differ from those associated with a change from the moderate to very high state of fitness.

Although numerous studies have reported a variety of adaptations to aerobic fitness training and detraining, it is difficult to comprehend how the individual adaptations interact to affect physiological systems. Changes in cardiac and vascular structure, baroreflex function, neuroendocrine and neural activity, blood volume and cardiac indices such as stroke volume all appear relevant and may affect orthostatic tolerance. Of the data examined it appears that those mechanisms most strongly associated with arterial pressure may have the greatest bearing on the issue i.e. baroreflex function and blood volume. In particular the number of studies suggesting the possibility of a relationship between baroreflex function and aerobic fitness indicates that if fitness is related to orthostatic tolerance the baroreflex system could be an associated mechanism. A mechanism potentially responsible for an alteration of baroreflex function with increased fitness is exercise training induced hypervolaemia. It may be, however, that if blood volume per se is associated with the issue there may be an optimal volume for aiding orthostatic tolerance beyond which other related factors may lead to a reduction in tolerance.

The contention by some authors that blood volume may be directly involved with the relationship between orthostatic tolerance/fitness (or exposure to microgravity or head-down tilt) suggests that should the baroreflex system also be relevant to the issue, it may be that the cardiopulmonary baroreceptors with their association with cardiac filling, are more relevant to the issue than arterial baroreceptors. Certainly an examination of relevant literature shows that the carotid baroreflex function/aerobic fitness relationship appears to be less clear than the apparent negative relationship between cardiopulmonary baroreflex gain and fitness.

With regards to microgravity the situation is reversed; data show a clear negative relationship between carotid baroreflex gain and exposure to microgravity or head-down tilt, however, insufficient data exists to draw a conclusion concerning the effects upon cardiopulmonary baroreceptor function. The fact that microgravity affects carotid baroreflex function after as little as 4 d in orbit may indicate that the effects upon the baroreflex system are relatively rapid.

To address the lack of clarity concerning the relationships between orthostatic tolerance and aerobic fitness and baroreflex function and in order to examine whether short duration exposure to microgravity affects the baroreflex response, this study aimed to ascertain whether a change in aerobic fitness would alter tolerance to LBNP, whether carotid and cardiopulmonary baroreceptor function would be affected by change in exercise trained state and whether the integrated baroreflex would be affected by change in exercise trained state and/or microgravity. To achieve this aim three questions were addressed.

- Does a change in exercise trained state result in a change in orthostatic intolerance?
- Do exercise trained individuals have altered baroreflex sensitivity during exposure to microgravity when they are highly trained compared to when they are detrained?
- Are the carotid and/or cardiopulmonary baroreceptor reflexes affected by trained state and if so, to what degree?

2.10 HYPOTHESES

- Endurance athletes exhibiting exercise-training induced hypervolaemia will show poorer orthostatic tolerance (as measured by progressive lower body negative pressure) in the trained state than in the detrained, euvolaemic state.
- Endurance athletes exhibiting exercise-training induced hypervolaemia will show less sensitive integrated baroreceptor function (less pronounced slowing of the heart for a given increase of arterial pressure) both at +1Gz and during microgravity in the trained state than in the detrained, euvolaemic state.
- Cardiopulmonary baroreceptor sensitivity will increase (greater peripheral vascular constriction for a given fall in central venous pressure) as a result of a reduction of endurance fitness sufficient to lower exercise-training induced hypervolaemia to euvolaemic levels.
- Carotid baroreceptor function will show no change as a result of a reduction of endurance fitness sufficient to lower exercise-training induced hypervolaemia to euvolaemic levels.

3.0 METHODS

3.1 PLAN OF INVESTIGATION IN GENERAL

Five assessments of physiological function were employed with a view to ascertaining whether exercise trained state affects orthostatic tolerance and/or baroreceptor function. The assessments were undertaken when the subjects were in a trained (fit) and detrained (unfit) state. The procedures adopted were; $\dot{V}O_2max$ to obtain a measure of aerobic fitness; closed-circuit carbon monoxide re-breathing to estimate blood volume; carotid sinus stimulation to measure carotid sinus baroreceptor gain; a combination of LBNP, venous occlusion plethysmography and central venous pressure measurement to assess cardiopulmonary baroreceptor gain, and an estimation of orthostatic tolerance by means of progressive LBNP. The principle physiological assessments were conducted over two days before and after a three-month period of training or detraining[9]. At the start of the conditioning period three subjects were fit and therefore detrained and five subjects were in a detrained state and subsequently retrained.

In addition to ascertaining the above measures, integrated baroreflex function at +1G and during microgravity was also measured, again both in trained and detrained states. Two series of parabolic flights were used to provide the microgravity environment. The flights were undertaken before and after the conditioning period. Valsalva's manoeuvres were used to obtain a measure of integrated baroreflex sensitivity during microgravity (in-flight) and when at 6° head-down tilt and seated at +1G (before and after flight).

Ethical Approval. An application to the King's College Research Ethics Committee for approval to conduct all aspects of the study was made during the preparatory phase of the project. The application included details of the risks and hazards of the procedures to be used, methods of recruiting subjects, choice of subject populations, poster and consent form and content of a letter sent to the subjects' family practitioner (Appendix A).

[9] Hereafter this period will be termed the conditioning period and refers to that period when a test subject either detrained or retrained or when a control subject continued normal activities between the two sets of measurements.

3.2 SUBJECTS.

Eight athletic test subjects (6 male, 2 female) and seven non-athletic control subjects (3 male, 4 female) aged between 20 and 33 yr were recruited from King's College London, the local student community and the local and national athletic community. Volunteers with a history of cardiovascular, respiratory and/or central nervous system disease or evidence of any other disease during clinical examination and a review of a 12 lead electrocardiogram were excluded. In relevant reviews of literature no indications were found that gender would affect longitudinal intra-subject comparisons, and thus both sexes were used. Informed written consent to participate in the study was obtained from all subjects. Appendix B contains the screening and consent forms used.

Test Subjects. All test subjects undertook and passed a Civil Aviation Authority class II medical examination and showed a normal asymptomatic response to a Valsalva's manoeuvre at 40 mmHg expiratory effort for 10 s. Test subjects were trained in the effects of ascent to and decent from 7800m in a hypobaric chamber, and of exposure to hypoxia by breathing air at an absolute pressure equivalent to an altitude of 7800m.

Acceptance Criteria:

- No history of cardiovascular, respiratory and/or central nervous system disease or evidence of any other disease.
- Normal arterial pressure (systolic pressure < 140 mmHg, diastolic pressure < 90 mmHg).
- Able to fit comfortably into the LBNP chamber used for the study.
- $\dot{V}O_2max$ values in the trained state equal to or greater than 60 $ml.kg^{-1}.min^{-1}$ for males and equal to or greater than 55 $ml.kg^{-1}.min^{-1}$ for females, or which had been measured to be at or above these levels in the past.

Control Subjects. Control subjects were recruited according to the same acceptance criteria as the athletes with the exception of that of fitness, which could be of any standard. Control subjects undertook the principle physiological assessments before and after a 'conditioning' period. The conditioning period in their case required them to maintain their normal activity levels and lifestyle. Due to the limitation of places for the parabolic flights, it was not possible to expose the control subjects to microgravity.

3.3 INVESTIGATION PHASES.

For planning and scheduling purposes the study was divided into 7 phases:

PHASE 1: *Technique Development and Validation* - The initial stage of the study involved the development and validation of the apparatus and techniques to be used. The primary experiments and results are contained within the text of this thesis, however, validation experiments and preliminary investigations are presented in the appendices.

PHASE 2: *Subject Recruitment And Training Period* - Subjects were actively recruited during phase 1 using posters and subject information sheets (Appendix D), but medical examinations and final selection were not undertaken until phase 2. Subjects who were recruited were trained in the techniques and procedures to be used during phase 3 and the subsequent physiological assessment.

PHASE 3: *First Series Of Parabolic Flights* - Subjects were exposed to short periods of microgravity (20 to 25 s) whilst on board European Space Agency Airbus A300 parabolic flights. Integrated baroreceptor sensitivity was assessed during this period. With the exception of one subject, each undertook one flight during which he/she performed five to eight Valsalva's manoeuvres whilst weightless. The subjects also performed three manoeuvres when at 6° head-down tilt and three whilst seated at +1G before and immediately after the flight. One subject flew on each of the three flights in order that the repeatability of the procedure could be ascertained.

PHASE 4: *First Series of Physiological Assessments.*

- Assessment of aerobic fitness by measuring $\dot{V}O_2max$.
- Measurement of blood volume by means of a carbon monoxide re-breathing technique.
- Determination of carotid baroreflex gain by applying graded suction to the neck.
- Determination of cardiopulmonary baroreceptor function by measuring changes in vascular resistance in the forearm produced by applying suction to the lower body by means of a LBNP chamber.
- Estimation of orthostatic tolerance by measuring the time to pre-syncope during incremental LBNP.

PHASE 5: *Conditioning Period* - The test group either ceased from undertaking physical training or re-embarked upon their usual personal training regimen for a period of no less than 10 wk. The $\dot{V}O_2$max and blood volumes of each test subject were measured approximately every 4 wk during the conditioning period. Control subjects maintained their normal daily activity level and had $\dot{V}O_2$max and blood volume measurements undertaken at the start and completion of the 'conditioning' period.

PHASE 6: *Second Series of Physiological Assessments* - A repeat of phase 4 was carried out to assess the function of high and low pressure baroreceptor groups, tolerance to progressive LBNP, blood volume and aerobic fitness level of the test subjects after they had altered their fitness accordingly (i.e. detrained or retrained) and of the control subjects.

PHASE 7: *Second Series Of Parabolic Flights* - A repeat of the physiological assessments carried out during phase 3 was undertaken by means of a second series of parabolic flights. The chronological order of the study phases is illustrated in Fig 3.1.

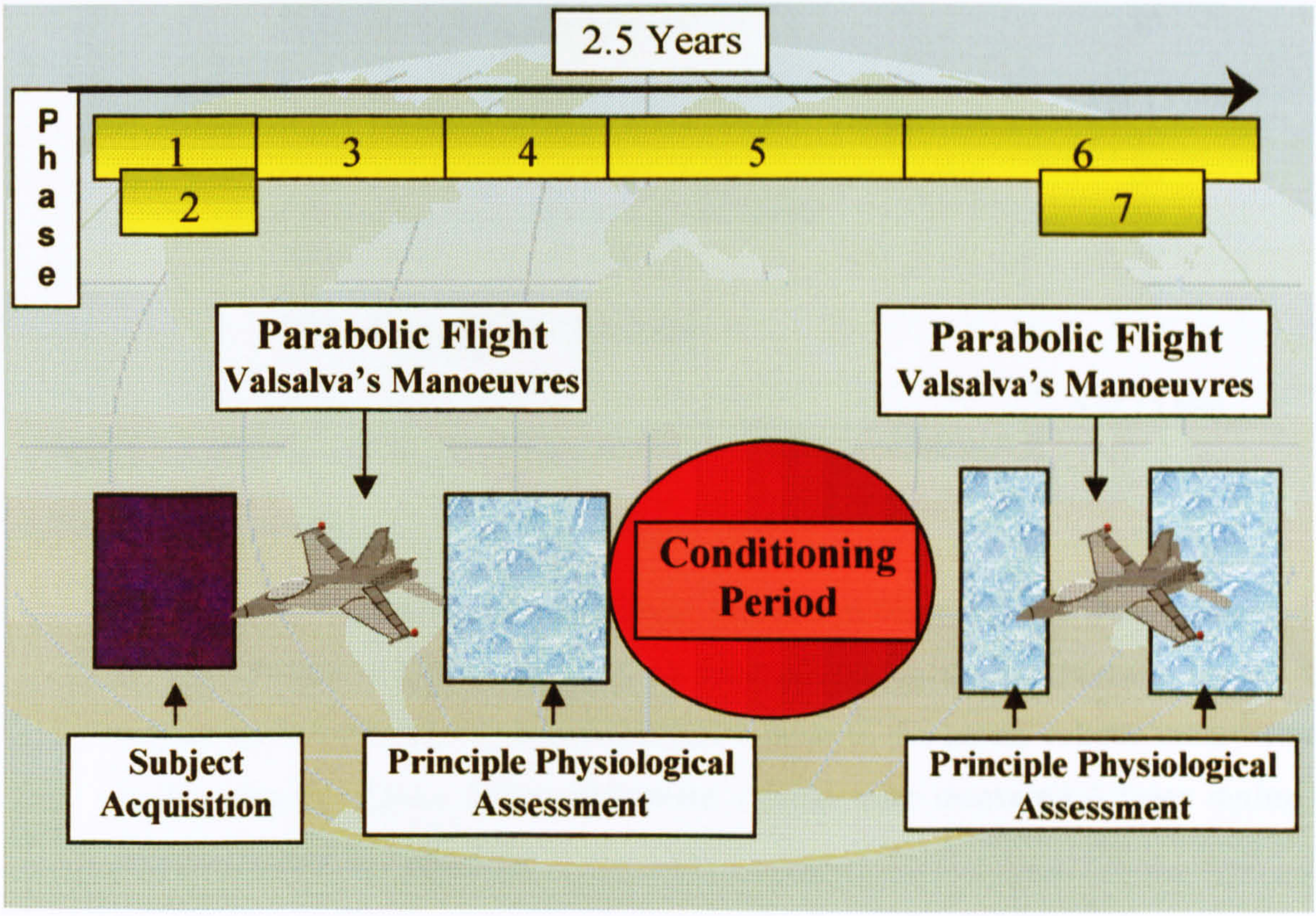


FIGURE 3.1 STUDY TIME LINE AND BROAD OUTLINE

3.4 PHYSIOLOGICAL ASSESSMENT.

Principle Physiological Assessment Schedule. The principle physiological assessments (Table 3.1) were conducted twice on all subjects, once before and once after the conditioning period. The assessments were conducted over two mornings or afternoons within 7 d of each other. The same order of assessments was used for each subject both before and after the conditioning period. Baroreceptor function was assessed twice both before and after conditioning. The first run in each case was used to familiarise the subject with the procedure, the second run provided the data for analysis.

Day	Activity/Assessment	Duration (min)
1	Medical examination (12 lead electrocardiogram)	15
	Paperwork and subject preparation	30
	Carotid Sinus Stimulation	30
	Cardiopulmonary Baroreflex Assessment preparation	60
	Cardiopulmonary Baroreflex Assessment	60
	Tolerance to progressive LBNP	30
	Total	3 hr 15 min
2	Carotid Sinus Stimulation	30
	Cardiopulmonary Baroreflex Assessment preparation	60
	Cardiopulmonary Baroreflex Assessment	60
	Maximum Oxygen Uptake	30
	Recovery	30
	Carbon-monoxide Re-breathing	45
	Total	4 hr 15 min

TABLE 3.1. PHYSIOLOGICAL ASSESSMENT PROTOCOL SCHEDULE

Follow-up Assessments.

Test Subjects. Follow-up assessments of fitness and blood volume were conducted on all test subjects at approximately 4 wk intervals during the conditioning period. The subject performed the $\dot{V}O_2max$ assessment prior to the blood volume measurement. In this manner subject fitness and blood volume were measured 4 times during the study as shown in Table 3.2.

	Parabolic Flight	Initial Assessment	Conditioning [10] Week 4	Conditioning [10] Week 8	Final Assessment	Parabolic Flight
Maximum Oxygen Uptake		√	√	√	√	
Carbon-monoxide rebreath.		√	√	√	√	
Carotid sinus stimulation		√√			√√	
Cardiopulmonary baroreflex assessment		√√			√√	
Tolerance to LBNP		√			√	
Integrated baroreflex assessment	√					√

LBNP = Lower Body Negative Pressure

√ = One assessment

TABLE 3.2. SUMMARY OF PHYSIOLOGICAL ASSESSMENTS UNDERTAKEN BY TEST SUBJECTS

Controls: It was anticipated that control subject fitness and blood volumes would not change significantly during their 'conditioning' period because of the maintenance of their normal level of activity. $\dot{V}O_2max$ and blood volume were therefore not measured during the condition period.

As a result of scheduling difficulties sub-maximal oxygen uptake assessments (pre and post-conditioning period) were conducted on two control subjects instead of $\dot{V}O_2max$ assessments. The sub-maximal assessments consisted of the same protocol as the $\dot{V}O_2max$ except that exercise was stopped when the heart rate reached 165 bpm. The pre and post maximum heart rate and oxygen uptake values achieved were compared to examine whether the aerobic fitness of the control subjects had changed during the conditioning period.

3.5 PROCEDURES

3.5.1 MEASUREMENT OF MAXIMUM OXYGEN UPTAKE.

$\dot{V}O_2max$ assessment was used to provide a quantitative measure of aerobic fitness. A protocol based upon the British Association for Sport and Exercise Science guidelines (BASES, 1988) was adopted. The aim of the assessment was to measure oxygen uptake,

[10] A mean of 12 ± 2.8 wk for controls and 17 ± 3.1 wk for test subjects.

carbon dioxide output and pulmonary ventilation when the subject was exercising at a maximal effort level. These measures enable the subject's maximum ability to utilise oxygen for energy production to be calculated.

Apparatus and Protocol. The subject completed an adapted Physical Activity Readiness Questionnaire (Fitness Canada, 1986) prior to the assessment. Providing no contraindications to maximal exercise were revealed by the answers to the questions the subject undertook the $\dot{V}O_2max$ assessment that day. The arrangement of the equipment employed is illustrated in Fig 3.2.

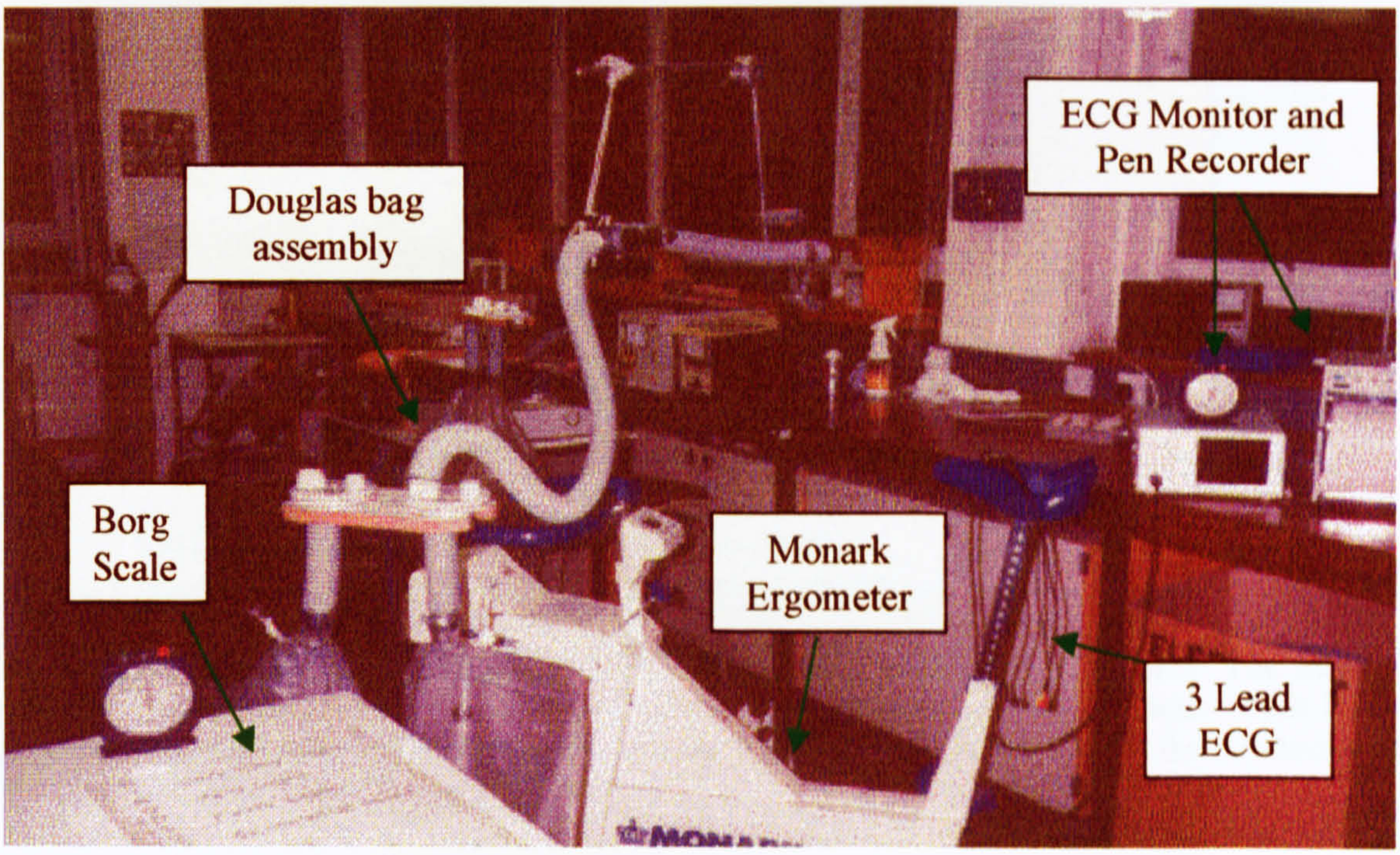


FIGURE 3.2. MAXIMUM OXYGEN UPTAKE APPARATUS.

A continuous protocol (Fig 3.3) was employed in which the subject maintained a pre-determined speed on a cycle ergometer (Monark Ergomedic 818E, Sweden) whilst the load was raised incrementally by increasing the tension of the resistance belt around the flywheel. The subject was allowed to warm-up for three to four min before starting the assessment by cycling at a work rate of between 25 and 50 Watts. The speed and the start work rate were chosen according to subject's perceived fitness (his/her own opinion), observed fitness

(warm-up) and the experience of the investigator and were usually 65 rpm and 100 Watts respectively. The intensity of exercise was raised every three min by increasing the load (flywheel friction) against which the subject had to cycle. Objective and subjective measures of workload were obtained by measuring heart rate using a 3 lead electrocardiograph (Cardiac Recorder series 5006, Enfield, UK) and by the subject indicating his/her perceived effort by means of a Borg scale (Borg, 1970) respectively.

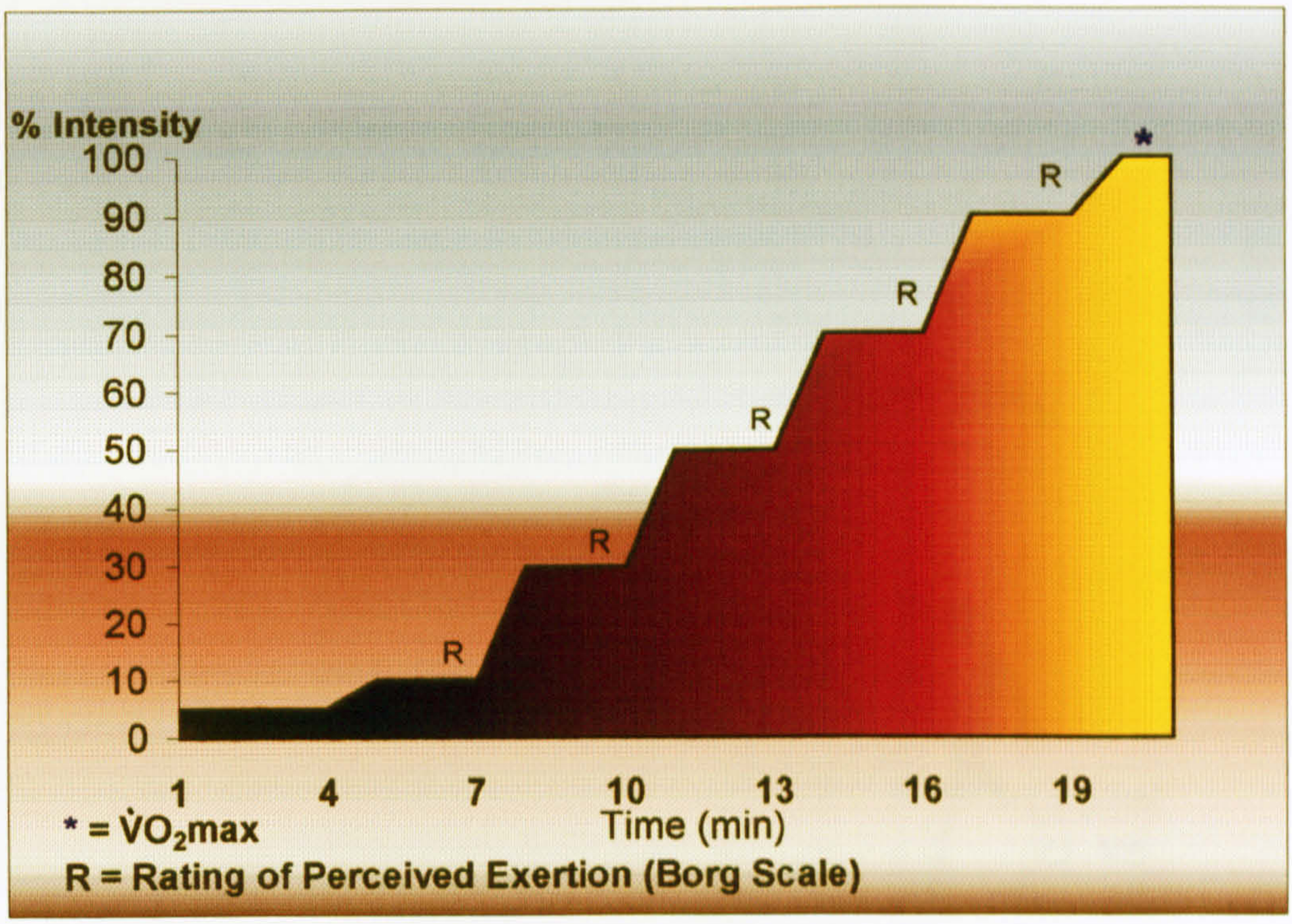


FIGURE 3.3 PROTOCOL FOR MEASURING MAXIMUM OXYGEN UPTAKE. The assessment required that the subject maintained a pre-determined speed on a cycle ergometer whilst load was increased incrementally by increasing the tension of the resistance belt around the flywheel every 3 min until volitional exhaustion was reached.

The subject breathed room air through a one-way valve box (SRI, Edenbridge, UK) and 50mm internal diameter tubing whilst wearing a nose clip. The subject was instructed to cycle until volitional exhaustion and to indicate when he/she was about one minute from stopping by pointing an index finger in the air. Expired air was collected in Douglas bags during the last 45 s of the stages in which the subject indicated that he/she had reached a rating of perceived exertion (RPE) greater than 14. The collection made during the last minute of exercise was subsequently used for analysis. Expired oxygen and carbon dioxide concentrations were measured using Servomex fast response analysers (Servomex Plc,

Crowborough, UK) using self-indicating anhydrous Calcium Sulphate (Dryrite, Poole, UK) to dry the gases. Expired gas volume was measured using a dry gas meter (Watson Marlow, London). The electrocardiogram was recorded using a two channel thermal recorder (Lectromed MX216, Lectromed Ltd, Jersey, Channel Islands). Lead II of a standard three lead configuration was used to monitor the electrocardiogram (Fig 3.4). On all occasions expired oxygen and carbon dioxide concentrations and Douglas bag volume were measured within 30 min of the end of the assessment, $\dot{V}O_2max$ was then calculated accounting for ambient temperature and barometric pressure.

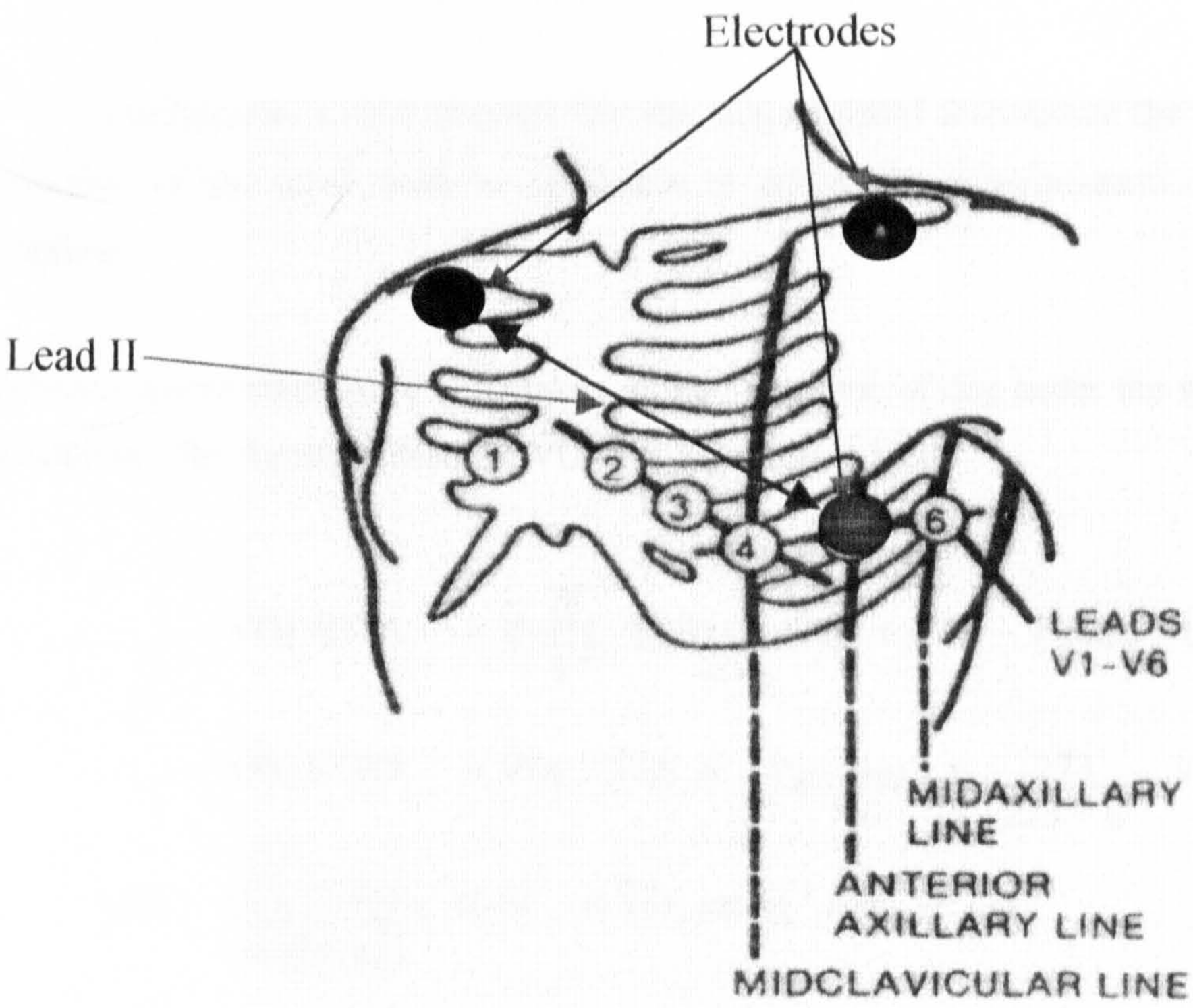


FIGURE 3.4 THE LOCATION OF ELECTROCARDIOGRAM ELECTRODES.

Cessation Criteria. The subject was provided with a safety brief prior to starting the test. The brief highlighted the fact that the subject should stop if he/she felt any;

- chest pains,
- difficulty in breathing,

- dizziness or light-headedness
- lack of coordination
- or for any other reason they wished to stop.

In addition the assessment would be stopped if the medical monitor present noted;

- any major electrocardiogram abnormalities such as abnormal rhythms or significant depression/elevation of ST-segments.
- signs of poor perfusion such as cyanosis or pallor.
- undue distress in any way other than through fatigue.

Furthermore it was stressed that the subject could discontinue the test by their own authority, at any point, with no obligation to inform the experimenters of the reason for stopping.

$\dot{V}O_2$max assessments were undertaken at the same time of day under the same experimental conditions. The formulae used for $\dot{V}O_2$max calculations were:

$$\dot{V}O_2 \text{ ATPS} = \dot{V}_E \left\{ \left[\frac{1 - F_EO_2 - F_ECO_2}{F_IN_2} \right] \times F_IO_2 - F_EO_2 \right\} \text{ l/min}$$

$$\dot{V}O_2 \text{ STPD} = \dot{V}O_2 \text{ ATPS} \times \frac{P_B - P_{H2O}}{760} \times \frac{273}{273 + t_r} \text{ l/min}$$

and $$\frac{\dot{V}O_2 \text{ STPD}}{\text{weight (kg)}} \times 1000 = \dot{V}O_2 \text{ ml.kg}^{-1}\text{.min}^{-1}$$

3.5.2 MEASUREMENT OF BLOOD VOLUME.

Blood volume was measured using a carbon monoxide re-breathing technique based upon the determination of the increase in carboxyhaemoglobin concentration in the blood resulting from the addition of a known amount of carbon monoxide to a closed breathing circuit. The concentration of carboxyhaemoglobin in the blood was determined from the partial pressure of carbon monoxide and the fractional oxygen concentration in alveolar gas whilst rebreathing 100% oxygen, assuming Haldane's first principle. The carboxyhaemoglobin in the blood was measured using this technique before and after the addition of a known quantity of carbon monoxide to a closed circuit containing 100% oxygen. A further rebreathing period provided confirmation that a steady value had been achieved. The measured increase in carboxyhaemoglobin due to the addition of carbon monoxide enabled total body haemoglobin to be estimated which, in combination with the measurement of blood haemoglobin concentration, enabled total blood volume to be calculated according to the known affinity of haemoglobin for carbon monoxide.

Apparatus. A closed circuit rebreathing system of approximately 5 l volume was constructed to enable an accurately measured volume (60 or 75 ml) of carbon monoxide to be introduced into the circuit containing 100% oxygen and a soda lime (Morgan Medical Ltd, Rainham, UK) canister to absorb carbon dioxide. Fig 3.5 illustrates the assembly in detail and Fig 3.6 illustrates the valve locations and direction of gas flow in the vicinity of the subject.

The apparatus consisted of a vertical tubing system containing the soda lime canister and two valve boxes. The valve box on the right arm of the circuit contained two one-way valves and a port leading to a three-way tap. The tap enabled the subject to breathe from room air, the circuit or the oxygen reservoir. Two non-return valves within a 'Y' piece located between the three-way tap and the oxygen reservoir allowed the subject to inspire oxygen and expire to room air. The second 'valve box' contained no valves and was therefore effectively a 'wide bore 'T' piece' situated at the bottom of the circuit to which a two-way tap was connected. Two 2.5 l anaesthetic bags (Ohmeda Health Care, Harlow, UK) were attached to the arms of the tap enabling one bag to be turned in to the system at any one time. Each bag had a Luer tap connection at one end to which fine bore (1mm diameter) tubing was attached. A port was drilled into the rear of the 'wide bore 'T' piece' into which a

three-way Luer tap was sealed. The tap enabled aliquots of carbon monoxide and a constant flow of oxygen at the subject's resting oxygen uptake to be added to the circuit. Gas within the circuit was sampled by carbon monoxide and oxygen analysers by means of tubing and ports from the anaesthetic bags, venting analysed gas to a waste bag.

A carbon dioxide analyser sampled respired gas from a port in the subject's mouthpiece for the measurement of end-tidal carbon dioxide partial pressure. Confirmation that the system was leak proof was made prior to each measurement by filling the circuit with oxygen. The anaesthetic bags in the system would remain inflated overnight if all seals were secure. Oxygen content within the circuit was also measured prior to each assessment to check for nitrogen ingress.

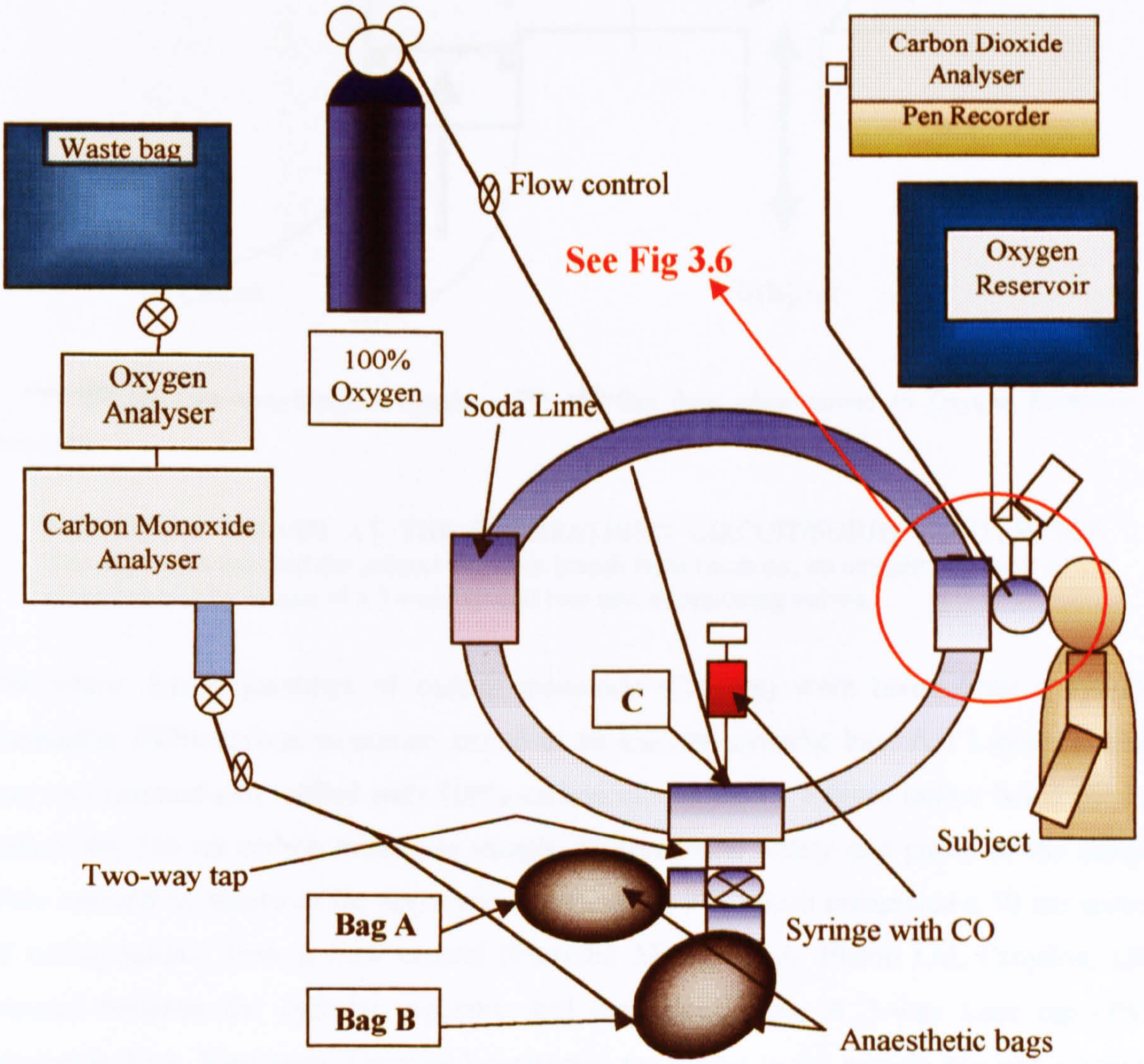
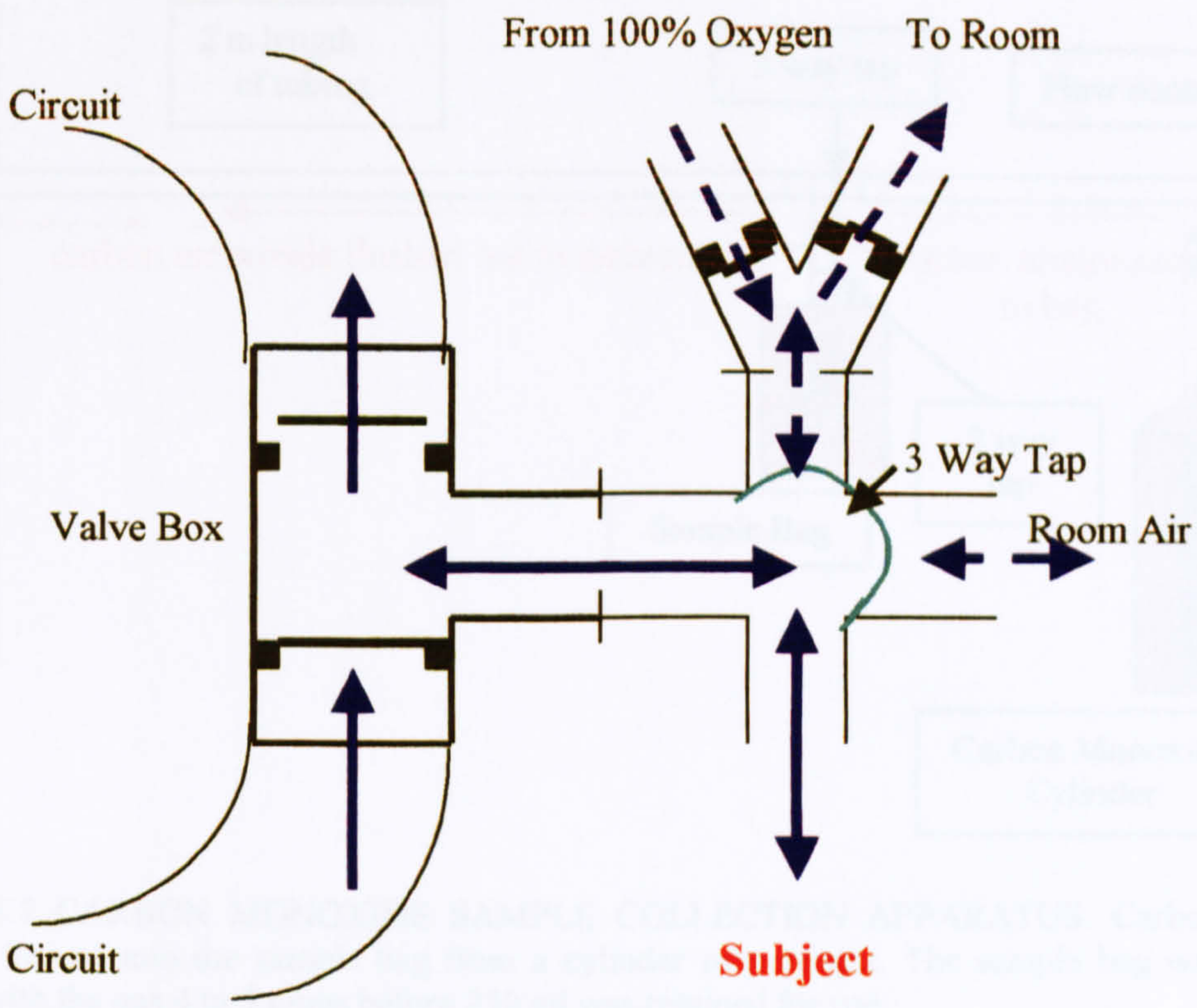


FIGURE 3.5 CARBON MONOXIDE REBREATHING APPARATUS. The subject rebreathed from either bag A or bag B. The bolus of carbon monoxide was injected at point 'C'.



→ Gas flow when turned to circuit — → Gas flow when turned to Oxygen Reservoir or Room Air

FIGURE 3.6 VALVES AT THE REBREATHING CIRCUIT/SUBJECT INTERFACE. The apparatus enabled the subject to either breath from room air, an oxygen reservoir or the closed circuit by means of a 3-way tap and two sets of opposing valves.

Procedure. Small quantities of carbon monoxide (250 ml) were taken from a cylinder containing 100% carbon monoxide stored in an external cylinder bay. A 1 l gas collection bag was emptied and refilled with 100% carbon monoxide 4 - 5 times before being used to collect the 250 ml carbon monoxide sample. Experimenter safety and purity of the sample were ensured by means of the apparatus shown in Fig 3.7, which comprised a 50 cm section of tubing leading from a flow control (Flowstat Minor, G. A. Platon Ltd, Croydon, UK) situated between the cylinder regulator and the sample bag. A 3-way Luer tap (PVB Medizintechnik, Kirchseon, Germany) connected the tubing to the sample bag and a second 2 m section of tube. The 2 m tubing lead to the outside of the cylinder bay so that flushing of the bag and tubing vented gas to atmosphere away from the investigator.

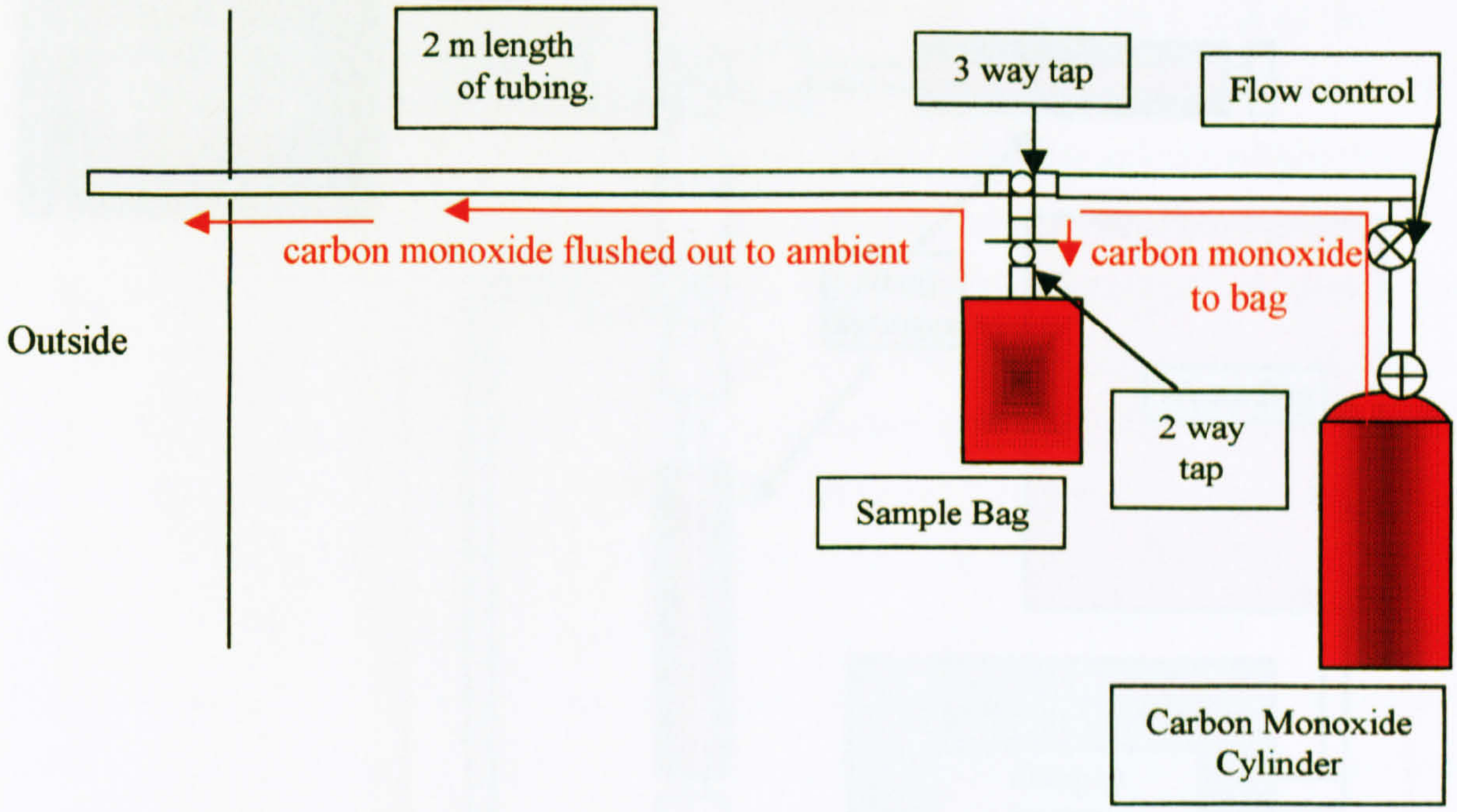


FIGURE 3.7 CARBON MONOXIDE SAMPLE COLLECTION APPARATUS. Carbon monoxide flowed into the sample bag from a cylinder of pure gas. The sample bag was 'flushed' with the gas 4 to 5 times before 250 ml was retained for use.

The sample bag filled with carbon monoxide was brought back to the laboratory and attached to two 3 way Luer lock taps (Fig 3.8). This system enabled quantities of carbon monoxide up to 50 ml to be drawn from the sample bag into syringes. The system was leak proof and with the exception of the last two aliquots, each sample of carbon monoxide was flushed from the Luer taps, through an oxygen analyser as a check of the purity of the gas[11] and then to a secure waste bag. This procedure was repeated a number of times to purge the system of air. Flushing continued until the oxygen concentration within the system was no greater than 0.1%. The waste bag was vented to the atmosphere outside the building on completion of the procedure.

[11] Presence of oxygen in the sample indicated contamination with air.

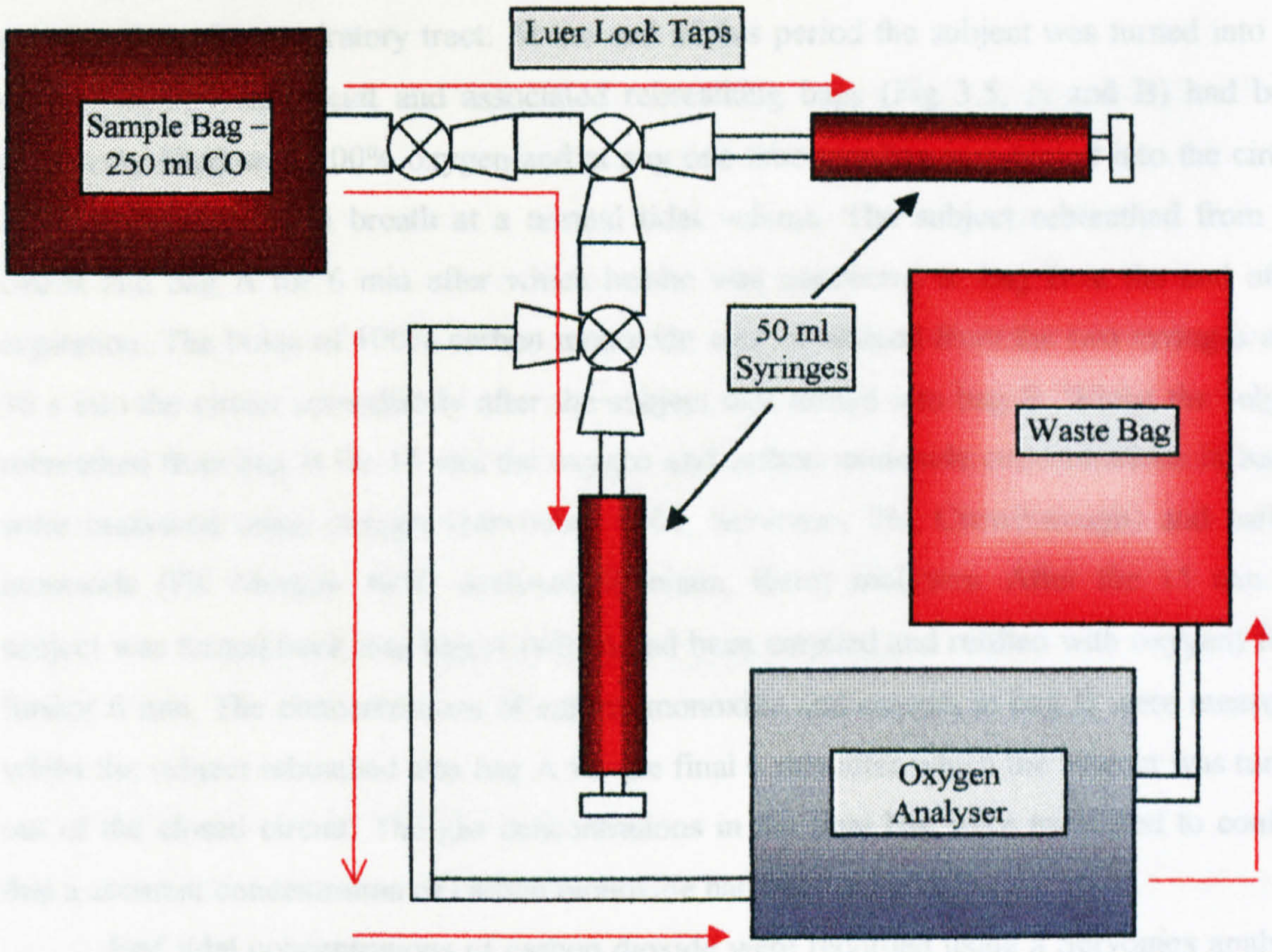


FIGURE 3.8 LUER LOCK TAP APPARATUS. 50 ml aliquots of gas were drawn into a syringe and then expelled through an oxygen analyser to a waste bag. When the gas contained less than or equal to 0.1% oxygen it was retained in the syringe for use. The same procedure was carried out for the second syringe, however, only 10 ml (for female subjects) or 25 ml (for males) was retained.

The final aliquots (50 ml and 10 ml for females and 50 ml and 25 ml for males) remained in the syringes and were taken from the analysis circuit to the re-breathing circuit in preparation for blood volume measurement.

Rebreathing Procedure. The circuit, including both rebreathing bags, was flushed and filled with 100% oxygen. Oxygen was added to the circuit at the subject's estimated basal rate of oxygen consumption, which was estimated by means of a standard body surface area nomogram and basal metabolic rate graph (McArdle et al., 1991).

The addition of oxygen and the absorption of carbon dioxide by the soda lime crystals enabled the circuit volume to be maintained at a constant level.

The subject breathed 100% oxygen from the open circuit (Fig 3.5) for 10 min order to wash nitrogen from the respiratory tract. At the end of this period the subject was turned into the closed circuit. The circuit and associated rebreathing bags (Fig 3.5, A and B) had been previously filled with 100% oxygen and at any one time one bag was turned into the circuit enabling the subject to breath at a normal tidal volume. The subject rebreathed from the circuit and bag A for 6 min after which he/she was connected to bag B at the end of an expiration. The bolus of 100% carbon monoxide was introduced from the two syringes over 30 s into the circuit immediately after the subject was turned into bag B. Whilst the subject rebreathed from bag B for 15 min the oxygen and carbon monoxide concentrations in bag A were measured using oxygen (Servomex 1400, Servomex Plc, Crowborough) and carbon monoxide (PK Morgan 403C analyser, Rainham, Kent) analysers. After the 15 min the subject was turned back into bag A (which had been emptied and refilled with oxygen) for a further 6 min. The concentrations of carbon monoxide and oxygen in bag B were measured whilst the subject rebeathed into bag A for the final 6 min after which the subject was turned out of the closed circuit. The gas concentrations in the final bag were measured to confirm that a constant concentration of carbon monoxide had been achieved.

End tidal concentrations of carbon dioxide were recorded using a Servomex analyser during the last minute of each stage in order to allow calculation of F_AO_2. Measurement of haemoglobin concentration using the cyanmethaemoglobin technique and spectrophotometry and total body haemoglobin by means of the rebreathing technique enabled blood volume to be calculated from the measured change in the carboxyhaemoglobin level.

Calibration of the carbon monoxide analyser was carried out using 0.3% carbon monoxide in air. The cylinder had a regulating valve attached and tubing leading from the valve to a Luer lock tap. Further tubing connected the Luer lock tap directly to the carbon monoxide analyser, the waste port from which was connected to a 50 l Douglas bag. Air was drawn through the tubing and analyser after carbon monoxide calibration thus flushing any remnant of carbon monoxide to the waste bag. The preliminary analyser reliability and circuit gas equilibration assessments are presented at Appendix E.

Calculations:

Appendix F contains an example of the calculations used to obtain blood volume. Carboxyhaemoglobin in the blood is calculated from the equilibrium concentration of carbon monoxide in the circuit which is equal to that in the alveolar gas (F_ACO_2) and the concentration of oxygen in the alveolar gas (F_AO_2) The latter is obtained from the FO_2 in the inspired gas (1.0) and the end-tidal concentration of carbon dioxide (F_AO_2) measured during the last minute of the equilibration period using the appropriate form of the alveolar gas equation. Haldane's first principle equation was used for the derivation of carboxyhaemoglobin concentration:

$$\frac{[HbCO]}{[HbO_2]} = M \times \frac{PCO}{PO_2} = M \times \frac{F_ACO}{F_AO_2} \qquad (1)$$

where M is the Haldane constant.

The measure of change in carboxyhaemoglobin required for the blood volume calculation was ascertained as follows:

$$[HbCO] = \frac{M \times \frac{F_ACO}{F_AO_2}}{1 + M \times \frac{F_ACO}{F_AO_2}} \qquad (2)^*$$

* For Derivation see Appendix F.

Calculation of Blood Volume

The difference between the [HbCO] in the blood before and after the addition of a known volume of carbon monoxide to the closed circuit and hence absorbed into the blood [the quantity of carbon monoxide remaining in the gas in the closed circuit and lungs is negligible] depends upon the total quantity of haemoglobin in the blood.

Since the carbon monoxide capacity of haemoglobin is 1.390 ml STPD of carbon monoxide per gramme of haemoglobin, the relationship between the quantity of carbon monoxide added to the blood (Vco) and the consequent increase in the concentration of Hb carbon monoxide (expressed as a percentage of the carbon monoxide capacity of the blood) will be

$$\text{Change in [HbCO]} = \frac{\text{VCO x 100}}{\text{Total Hb x 1.39}}$$

Whence

$$\text{Total Body Haemoglobin} = \frac{\text{VCO x 100}}{\text{Change in [HbCO] x 1.39}}$$

The blood volume is then calculated from the total quantity of haemoglobin and the concentration of haemoglobin in the blood determined from the venous blood sample assuming that the whole body haematocrit equals that of the venous blood sample

$$\textbf{Blood volume (litre)} = \frac{\text{Total Haemoglobin (g)}}{\text{Haemoglobin concentration (g/l)}}$$

Haemoglobin Concentration Measurement. The concentration of haemoglobin in 2 ml of whole blood was measured using the Drabkins cyanmethaemoglobin method (Diagnostic Reagents Ltd, Thame, UK). A 5 ml syringe was used to collect the blood sample either from a 32mm, 21 gauge cannula (Vasculon, Ohmeda, Harlow, UK) inserted into an antecubital vein in the right arm prior to cardiopulmonary baroreceptor function assessment, or directly from an antecubital vein using a 21 gauge needle and syringe.

Protocol. A 5 ml syringe was lubricated with heparin solution (5000 U/ml). An aluminium washer was inserted into the barrel of the syringe to aid mixing. A 2 ml sample of whole blood was taken from the subject under sterile conditions. The syringe and blood was placed in a vertical, rotary blood mixer (HR Flow Inducer, Watson Marlow, UK) until analysis was conducted, which was normally within 2.5 hours of sample collection.

4ml aliquots of Drabkins solution (Diagnostic Reagents Ltd, Thame, UK) were measured into five 5 ml cuvettes using a Gilson 5000 pipette (Anachem Ltd, Luton). A 20 µl sample of whole blood was pipetted into 4 of the cuvettes using a Gilson 250 pipette (Anachem Ltd, Luton). The blood and Drabkins solution in each cuvette was agitated to ensure complete mixing. All cuvettes and their contents were left to stand inside a 'light-tight' box for 20 min. The cuvette of Drabkin's solution without blood and cuvettes of 3 Drabkins standards (3.0, 11.5 and 18 $g.dl^{-1}$) were used to calibrate a UV/Vis spectrophotometer (Pye Unicam SP8-100). The spectrophotometer was set to measure light absorbance at a wavelength of 540nm. Appendix F contains a typical calibration plot. The absorbance at 540nm of each of the four cuvettes containing blood was measured in turn. The mean value of the four measurements was used to read off the concentration of haemoglobin from the calibration curve.

3.5.3 ASSESSMENT OF THE CAROTID SINUS BAROREFLEX

Controlled stimulation of the carotid baroreceptors was produced by applying suction to the neck over the sinuses. The affect of the stimulation was measured by recording the changes in R – R interval from an electrocardiogram. The measure of baroreceptor function used was the relationship between the magnitude of neck suction and the subsequent change in heart rate (the R - R interval response).

Apparatus. The stimulation apparatus (Fig 3.9) comprised a pair of plastic cups connected through a rapidly opening solenoid operated valve (A. Schvaders & Son, 13VA, 44W AC) to a vacuum source. The opening of the suction valve was initiated after a preset delay by a signal from the R-wave of the electrocardiogram. The suction valve remained open for a preset time and then closed. Subsequently a second solenoid-operated valve (the air inlet

valve) opened and allowed air to enter the system so that the pressure in the cups returns to atmospheric. The air inlet valve was closed whenever the suction valve opened.

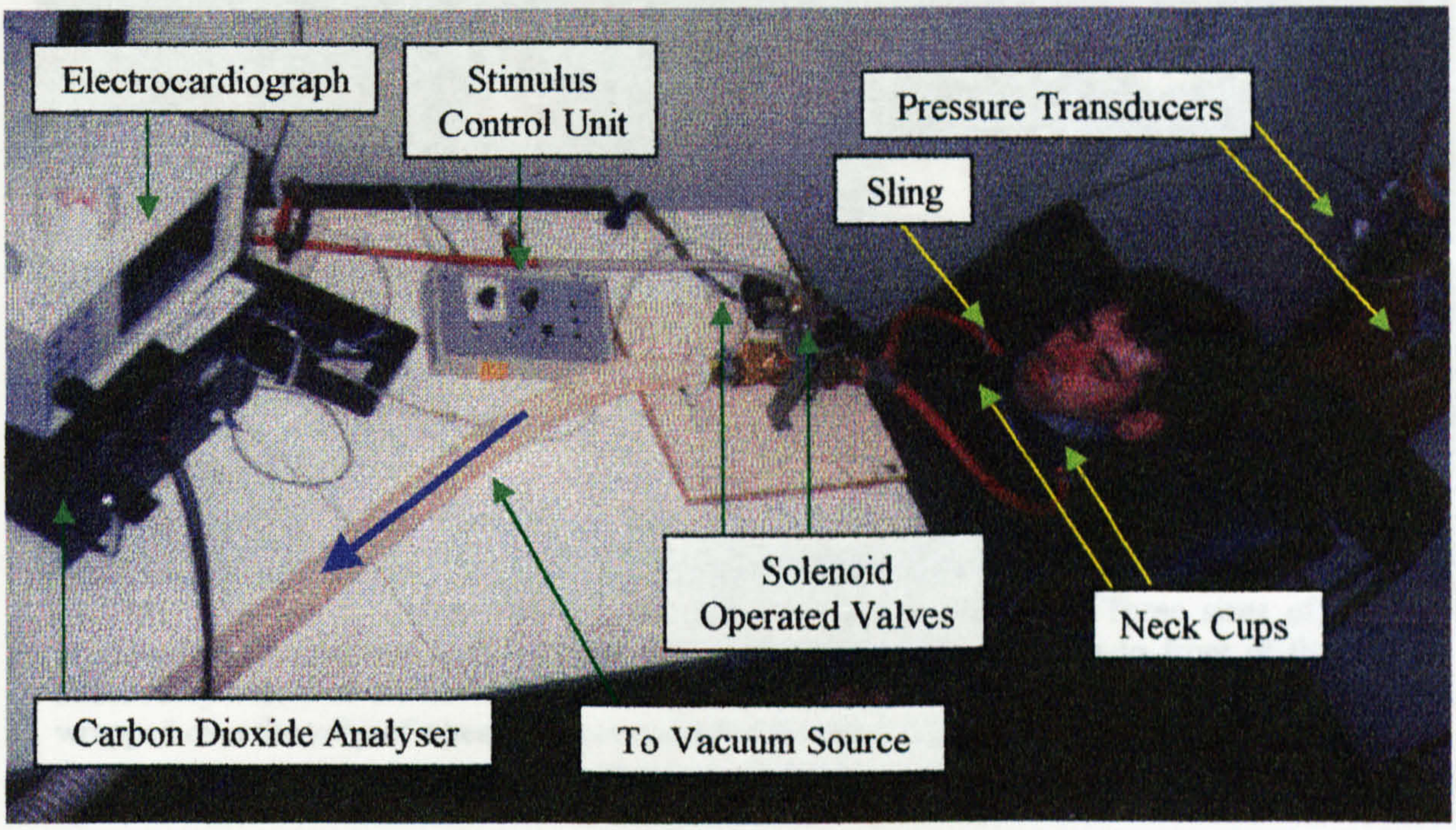


FIGURE 3.9 CAROTID SINUS STIMULATION SYSTEM. Depression of a button on the control unit activated the valves after a preset time interval after the next R wave. Vacuum was then transferred to the cups for a preset duration after which the valves were returned to their standby orientation (vacuum valve closed, air inlet valve open).

The neck cups were plastic half spheres with a small semi circular section cut away on one side and a slightly larger section cut away opposite the first (Fig 3.10). A 2 cm thick strip of blue-tac (Evostick, Stains) was placed around the rim of each cup. Six millimeter and 1mm internal diameter outlets enabled suction to be applied and pressure to be measured respectively. Three sets of cups were made (large, medium and small) to fit different size necks. The cups were held onto the neck by a canvas and Velcro sling which had been fabricated to fasten behind the neck and over the head (Fig 3.10).

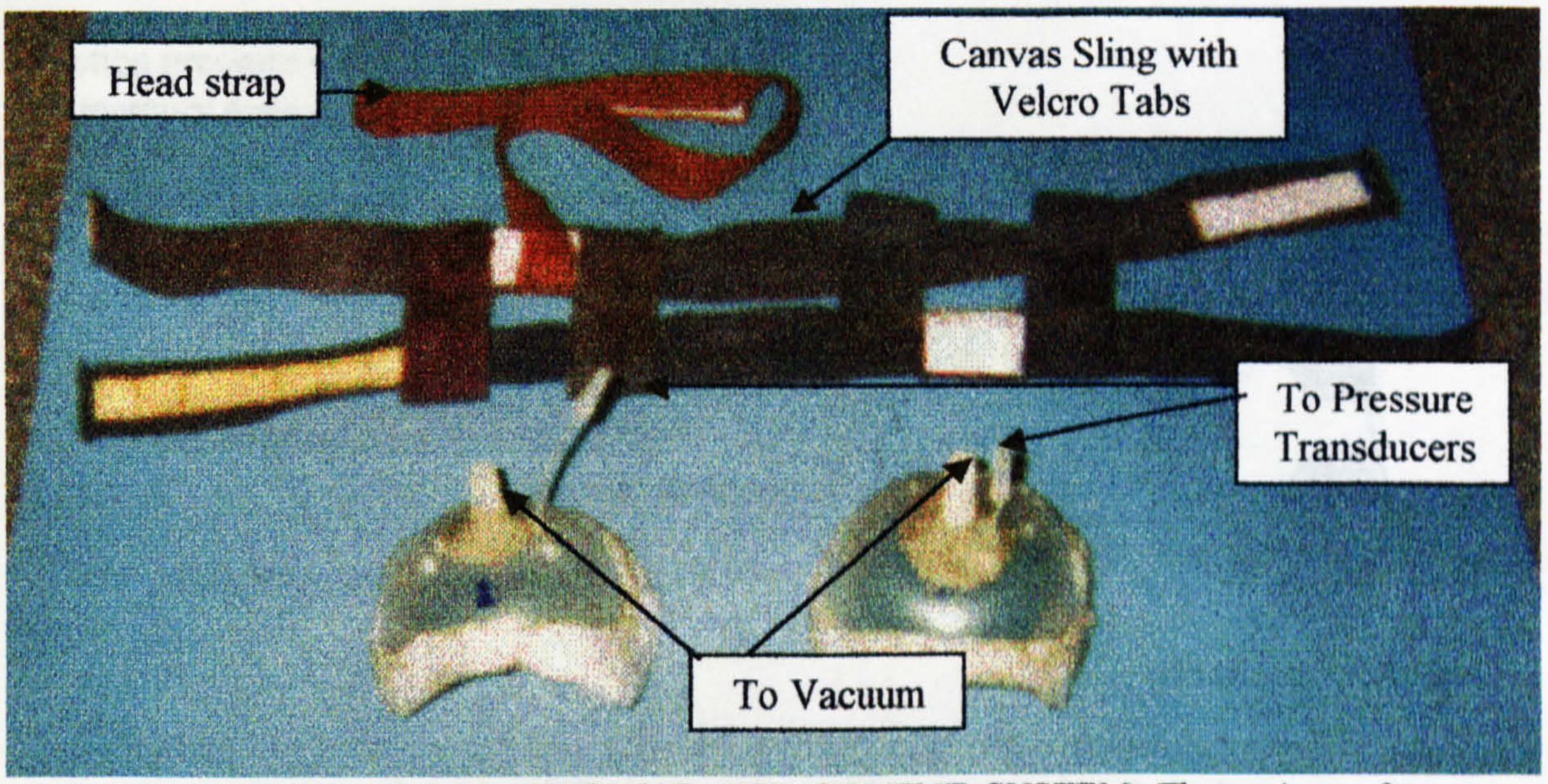


FIGURE 3.10 NECK CUPS AND SLING ATTACHMENT SYSTEM. Three sizes of cups were produced to fit different sizes of neck. The canvas sling held the cups to front of the neck and attached by velcro at the back of the neck. A strap was connected to one side of the sling and was wrapped over the subject's head and connected to the other side to support the weight of the cups.

After the cups were fitted the subject sat in a semi-reclined position. The cups were connected via 12 mm internal diameter, rubber tubing to a plastic 'Y' piece of the same diameter. The 'Y' piece was attached to 23 mm copper piping which lead to one side of a 25 mm internal diameter solenoid valve (valve A). The other end of this valve was connected to a vacuum source by means of a 4.5 m length of 35 mm diameter flexible tubing. A 20 mm bore solenoid valve (valve B) was connected perpendicularly to the copper pipe. The control of the valves was arranged so that when one was open the other was closed. Suction to the chamber of valve 'A' was applied by a Dymax pump via tubing from a drilled hole in the top of the valve chamber. This suction enhanced the speed of opening of the valve. On activation of the valves the vacuum source to A was directed to the cups. An electronic control box provided a means of varying the interval between the R signal of the ECG and opening of valve A and closure of valve B and the time for which the positions of the valves were maintained (Fig 3.12). The main vacuum source used was a BVC industrial vacuum cleaner (700W industrial vacuum cleaner, BVC Engineering Ltd Leatherhead). The strength of vacuum was controlled by means of an electric variac (0-270W Variac, Zenith, London, UK) which enabled the appropriate level of suction to be used at any given point in the protocol.

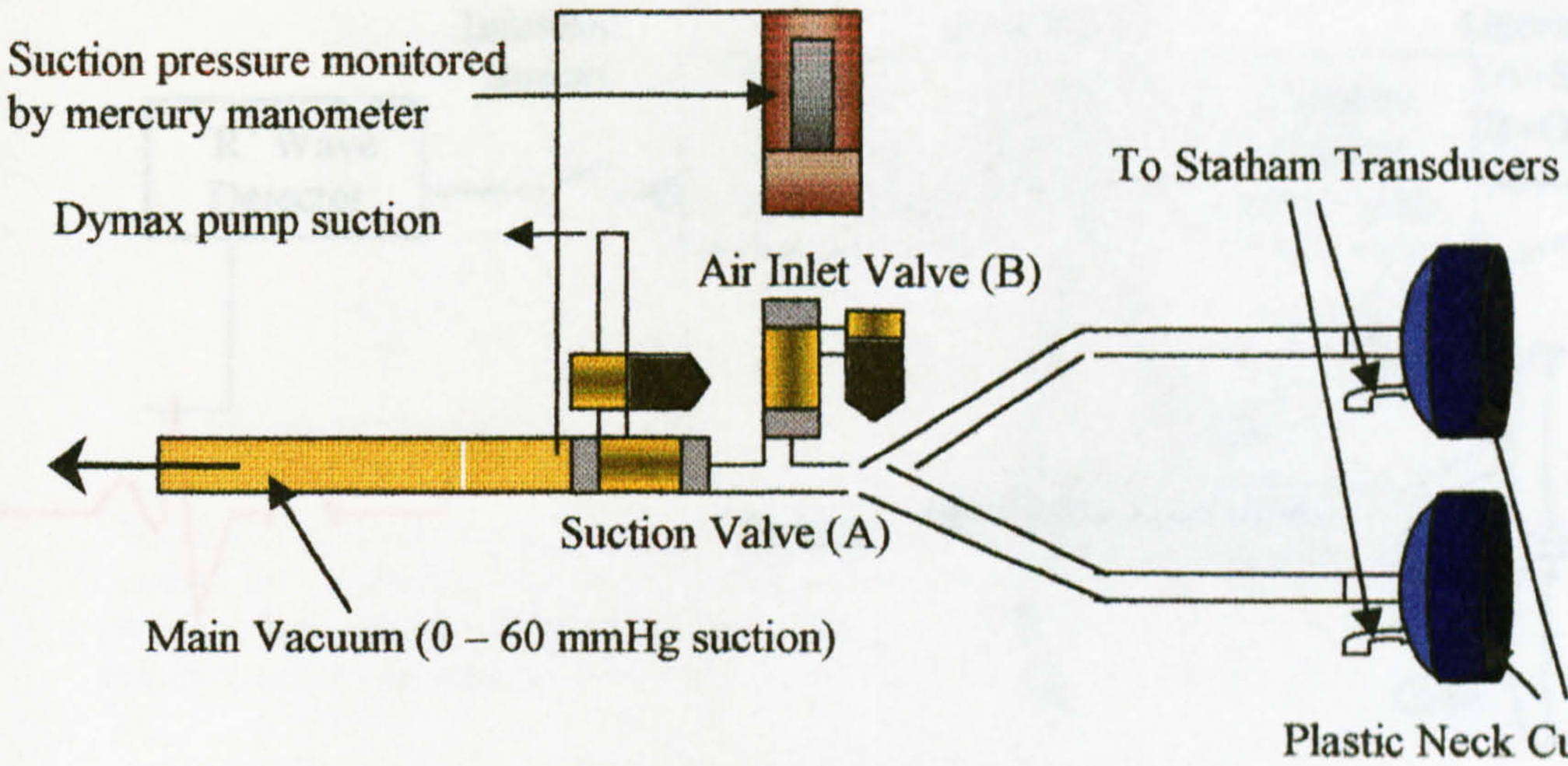


FIGURE 3.11 NECK CUP AND SOLENOID VALVE CONFIGURATION. During experimentation valves A and B were configured in opposition so that when one was open the other was closed, therefore exposing the interiors of the cups either to the vacuum source or ambient atmosphere.

Fig 3.12 shows the manner in which the control unit activates valves A and B in opposition. The variables examined during validation of the procedure were intensity, duration, timing and rate of application of the stimulus (Appendix I). The apparatus developed enabled a suction of 15 to 60 mmHg to be applied for 0.3 to 3.0 s at a rate of application > 400 $mmHg.s^{-1}$. The point of stimulation could be varied to occur between 0.04 and 0.34 s after a given 'R' wave in order that the stimulus was delivered 0.75 s before an anticipated 'P' wave. Appendix O outlines a validity study for the apparatus.

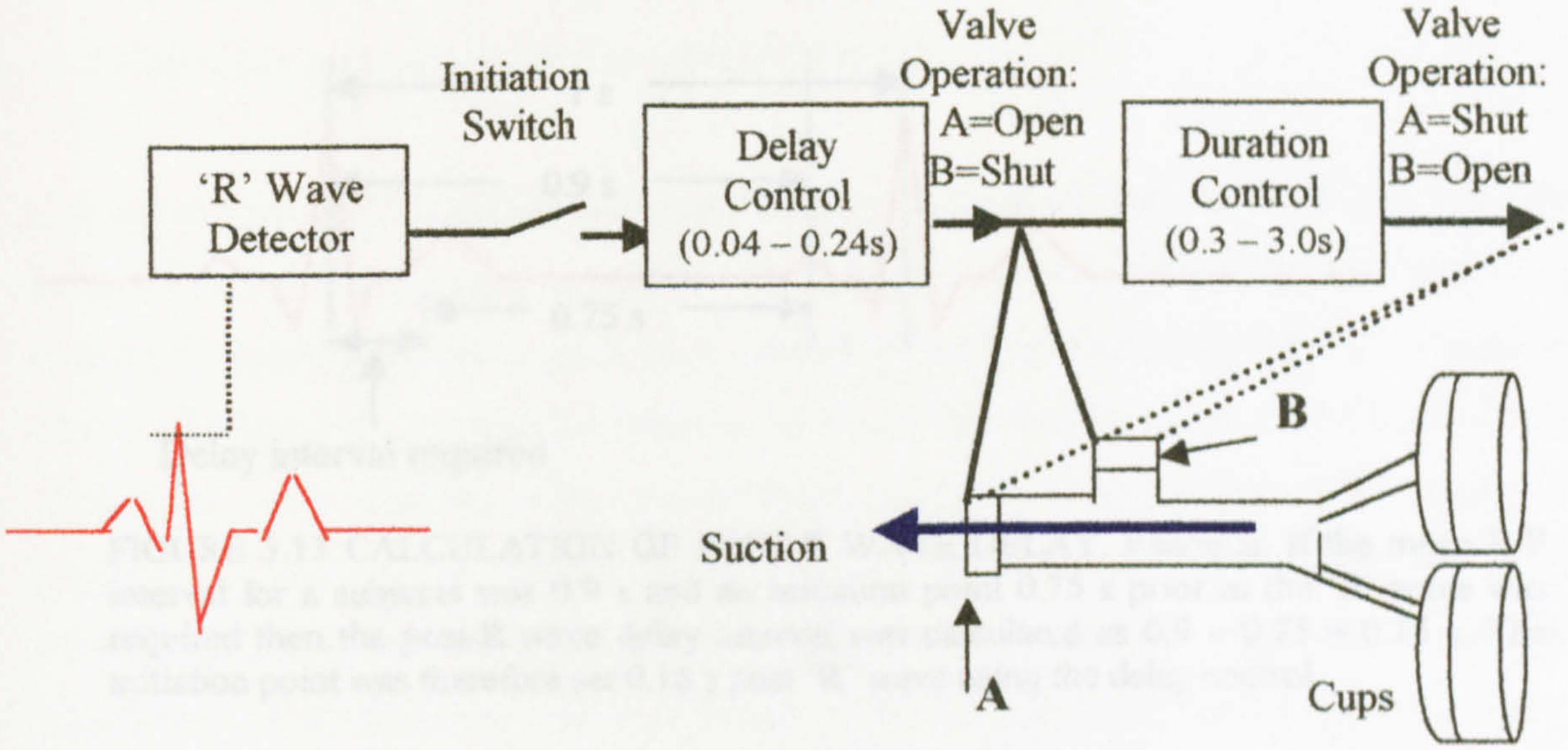


FIGURE 3.12 CAROTID SINUS STIMULATION CONTROL UNIT FUNCTION. The control unit continually detects the electrocardiograph 'R' waves. When the initiation switch is depressed the unit delays activation of the solenoid valves for a preset period. On activation, the suction valve opens and air inlet valve closes. The control unit 'deactivates' the valves after the preset delay period.

The post 'R' wave delay was calculated and set according to the subject's mean resting R-R interval calculated from 10 heart beats immediately prior to each assessment (Fig 3.13). The duration of stimulus was maintained throughout at 0.6 s. The rate of application of suction was affected by the level of suction, the tightness of seal of the cups and the volume within the cups, which differed slightly between subjects. The use of suction greater than 20 mmHg always resulted in application rate greater than 400 $mmHg.s^{-1}$. However, application rates of 400 $mmHg.s^{-1}$ for suctions less than 20 mmHg were not always possible. In these circumstances the fit and seal of the cups were adjusted until an application rate greater than 400 $mmHg.s^{-1}$ was achieved for a pressure between –15 and –20 mmHg. For some subjects this was at a pressure of –15 mmHg but for most occurred at a pressure of about –17 mmHg.

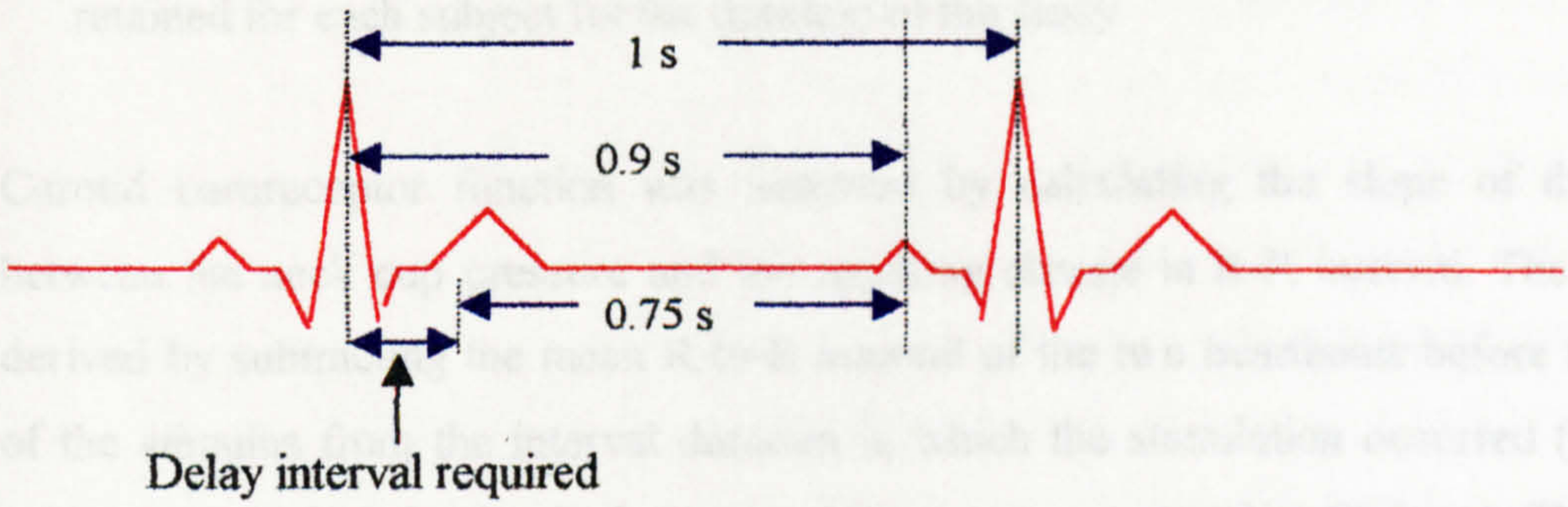


FIGURE 3.13 CALCULATION OF POST-R WAVE DELAY. Example: If the mean R-P interval for a subjects was 0.9 s and an initiation point 0.75 s prior to the 'P' wave was required then the post-R wave delay interval was calculated as 0.9 – 0.75 = 0.15 s. The initiation point was therefore set 0.15 s post 'R' wave using the delay control.

The suction applied to the neck was monitored by means of a mercury manometer. The pressure within each neck cup was measured by a Statham transducer (0-100 mmHg P23 ID, Gould, Ilford, UK) via 1 mm diameter tubing (Portex series 200/490/150, Portex Ltd, Hythe, UK). The electrical activity of the heart was monitored by lead II of a standard 3 lead electrocardiograph (Series 5006, Cardiac Recorders Ltd, Enfield, UK). Respiration was monitored by attaching the tip of the sampling catheter of a rapid response carbon dioxide analyser (Series 1400, Servomex Plc, Crowborough, UK) below the subject's nostril. All variables were recorded on a Chart 3.52 software package (AD Instruments, Hastings, UK) via Maclab 4/e biological analysis hardware (AD Instruments, Hastings, UK). The procedure used was:

- The neck cups were fixed over the positions of the right and left carotid sinus.
- A 3 lead electrocardiograph was attached to the subject's chest to record pulse interval.
- Fine bore tubing was attached below the subject's nose to monitor the concentration of carbon dioxide.
- Applications of suction occurred whilst the subject lay reclined at rest.
- All applications were made during expiration.
- Four trains of suction (17, 30, 45, 60 mmHg) were applied over approximately 30 min.
- Each suction train consisted of between 8 and 14 applications over approximately 3 min.
- A minimum interval of 10 s was allowed between each application.

- The order of the trains was randomised between subjects, but the same order was retained for each subject for the duration of the study.

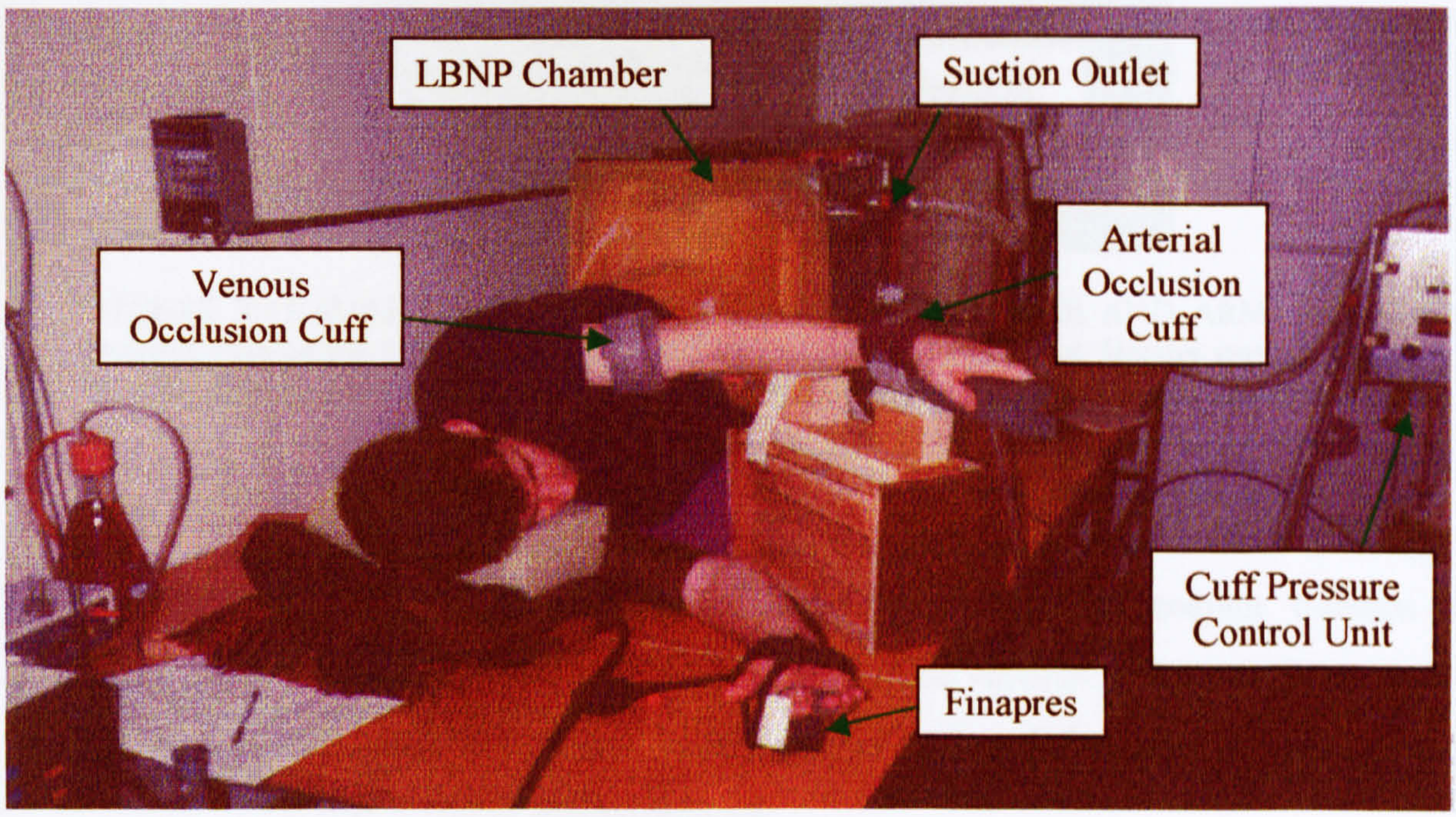
Carotid baroreceptor function was assessed by calculating the slope of the relationship between the neck cup pressure and the resulting change in R-R interval. The response was derived by subtracting the mean R-to-R interval of the two heartbeats before the application of the stimulus from the interval duration in which the stimulation occurred (or the interval subsequent to the stimulus in the case of heart rates greater than 80 bpm). The mean of the responses to the 8 – 14 stimuli for a given suction was used in calculations. A given relationship consisted therefore of four points each being the mean of a number of stimulations. The procedure was undertaken twice, the data from the second being used for the subsequent analysis.

3.5.4 ASSESSMENT OF THE CARDIOPULMONARY BAROREFLEX.

Cardiopulmonary baroreceptor reflex sensitivity was ascertained by applying suction to the lower body using a LBNP chamber and recording changes in central venous pressure and forearm blood flow. This procedure employed three techniques; central venous pressure was measured using the Gauer and Sieker (1956) method, forearm blood flow was determined by venous occlusion plethysmography and changes in central venous pressure were derived by the application of LBNP.

Outline of Procedure. The subject lay on his/her right side within the LBNP chamber with cushions supporting the upper body. Arterial pressure was measured during a 20 min rest period by means of a Finapres (Ohmeda 2300, Ohmeda Health Care, Harlow, UK) and manual auscultation (Fig 3.14). Towards the end of this period 20 mmHg LBNP was applied and arterial pressure recorded to confirm that mean arterial pressure was not affected by the depressurisation (a preliminary assessment of the effect of mild LBNP on arterial pressure can be seen at Appendix P). After the baseline period the Finapres cuff was removed and a 21-gauge cannula was inserted into an antecubital vein of the right arm. The cannula was connected to a Statham pressure transducer. The subject then passed the right arm through a

hole in the LBNP table, placing the right hand in an adjustable sling beneath (Fig 3.15). Having adopted this position eight forearm blood flow measurements were made with the LBNP chamber at ambient pressure. Two min after the last blood flow measurement the chamber pressure was reduced for 3 ½ min by one of four pressures; 5, 10, 15 or 20 mmHg. Forearm blood flow was measured eight times during this period. At the end of the LBNP a rapid re-pressurisation (~45 $mmHg.s^{-1}$) was achieved by disconnecting the vacuum hose from the chamber. The procedure was repeated three further times at each level of suction. A final set of blood flow measurements was conducted with the LBNP chamber at ambient pressure two min after the last application of suction.



FIGURES 3.14 BASELINE ARTERIAL PRESSURE MEASUREMENT PRIOR TO LOWER BODY NEGATIVE PRESSURE. Arterial pressure was measured from the right arm prior to cardiopulmonary baroreflex measurement and forearm blood flow from the left arm throughout the measurement.

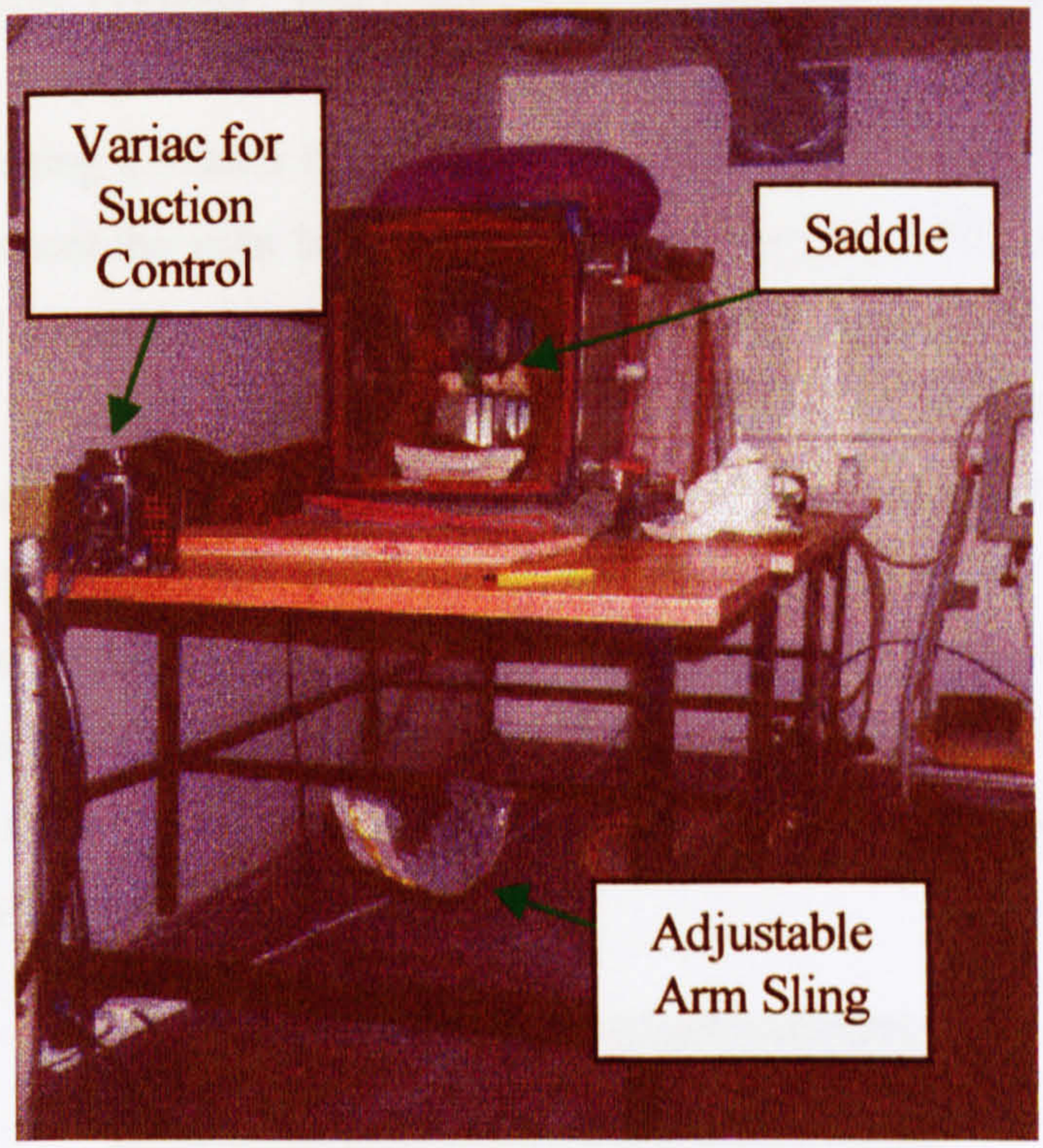


FIGURE 3.15 SUBJECT ENTRY POINT FOR LBNP CHAMBER AND ARM SLING. The subject entered the LBNP chamber before the cannula was inserted. He/she was instrumented and then allowed to rest for 20 min before the experimental procedures were started.

Throughout the procedure venous pressure, electrocardiogram, forearm blood flow and LBNP chamber pressure were recorded by means of the Chart 3.52 software package via Maclab 4/e biological analysis hardware. Cardiopulmonary baroreceptor function was derived from the relationship between changes in forearm vascular resistance (determined by dividing mean arterial pressure by forearm blood flow) and the central venous pressure produced by the four levels of suction applied.

Lower Body Negative Pressure. The LBNP technique involved placing a chamber over the lower body of the subject. An airtight seal was made around the subject's waist at the level of the iliac crests using a silicon rubber skirt (Fig 3.16). The chamber was oriented so that the subject could adopt the right lateral decubitus position (Fig 3.17). A wooden diaphragm was placed around the subject's waist under the rubber skirt to prevent the skirt being drawn into the chamber when the chamber pressure was reduced. When the subject lay in the chamber the diaphragm fitted snugly into the open end of the chamber. Elastic cord sealed the lower edge of the rubber skirt to the outside of the box (Fig 3.17).

A 'wooden saddle' (Fig 3.15) divided the top of the chamber in to two so that the legs were separated and the pelvis was held in position during suction. A padded wooden block was placed under the left ankle (Fig 3.18) so that the leg could be relaxed without the central wooden bar impeding blood flow.

FIGURE 3.16 SUBJECT WEARING A RUBBER LBNP SEAL. The small opening of the latex rubber skirt formed a seal around the subject's waist. The large opening fitted around the end of the LBNP chamber.

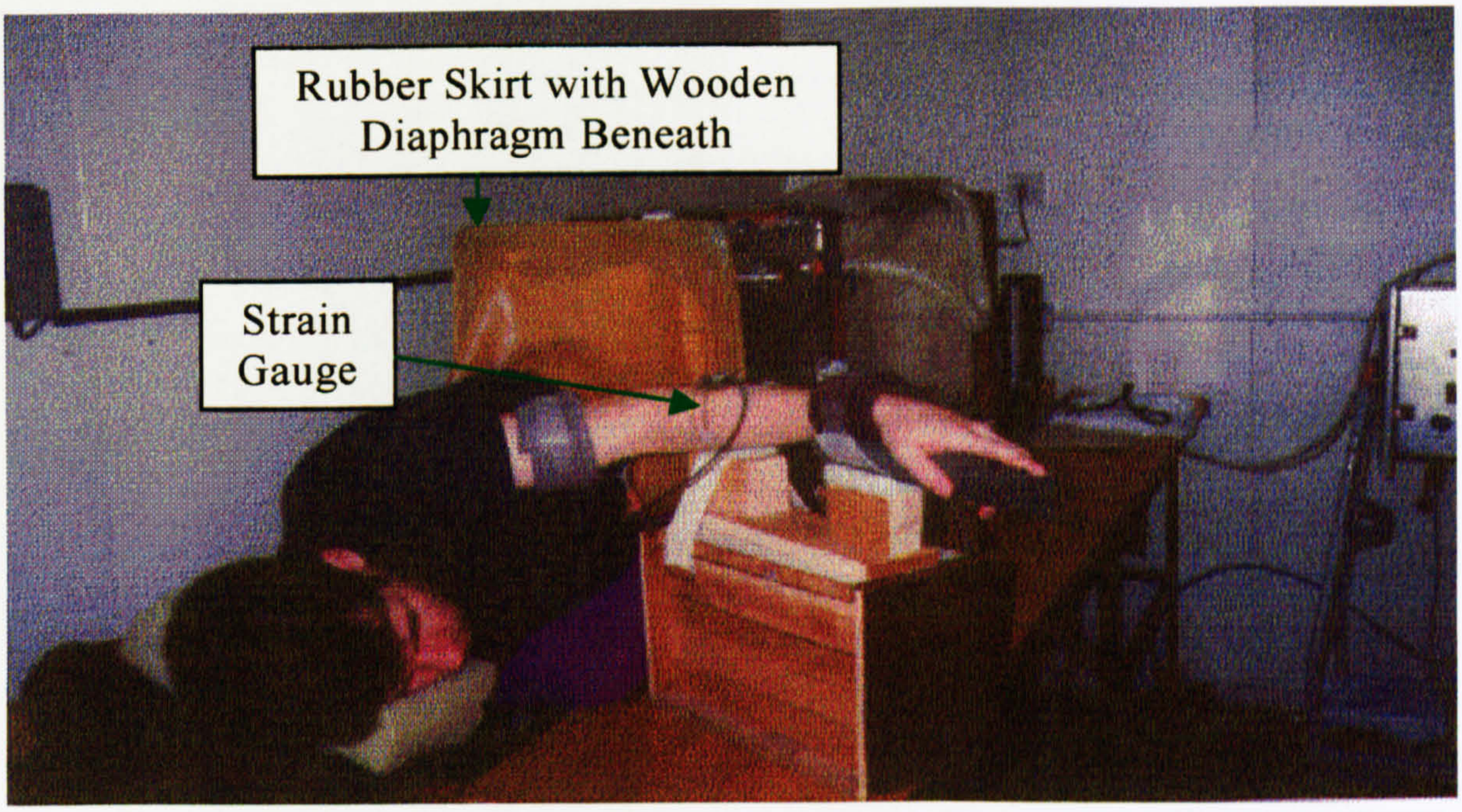


FIGURE 3.17 SUBJECT ADOPTING THE RIGHT LATERAL DECUBITUS POSITION WITHIN LOWER BODY NEGATIVE PRESSURE CHAMBER. The right arm hung below the body suspended by the wrist using an adjustable sling. Central venous pressure was measured from an antecubital vein in the same arm.

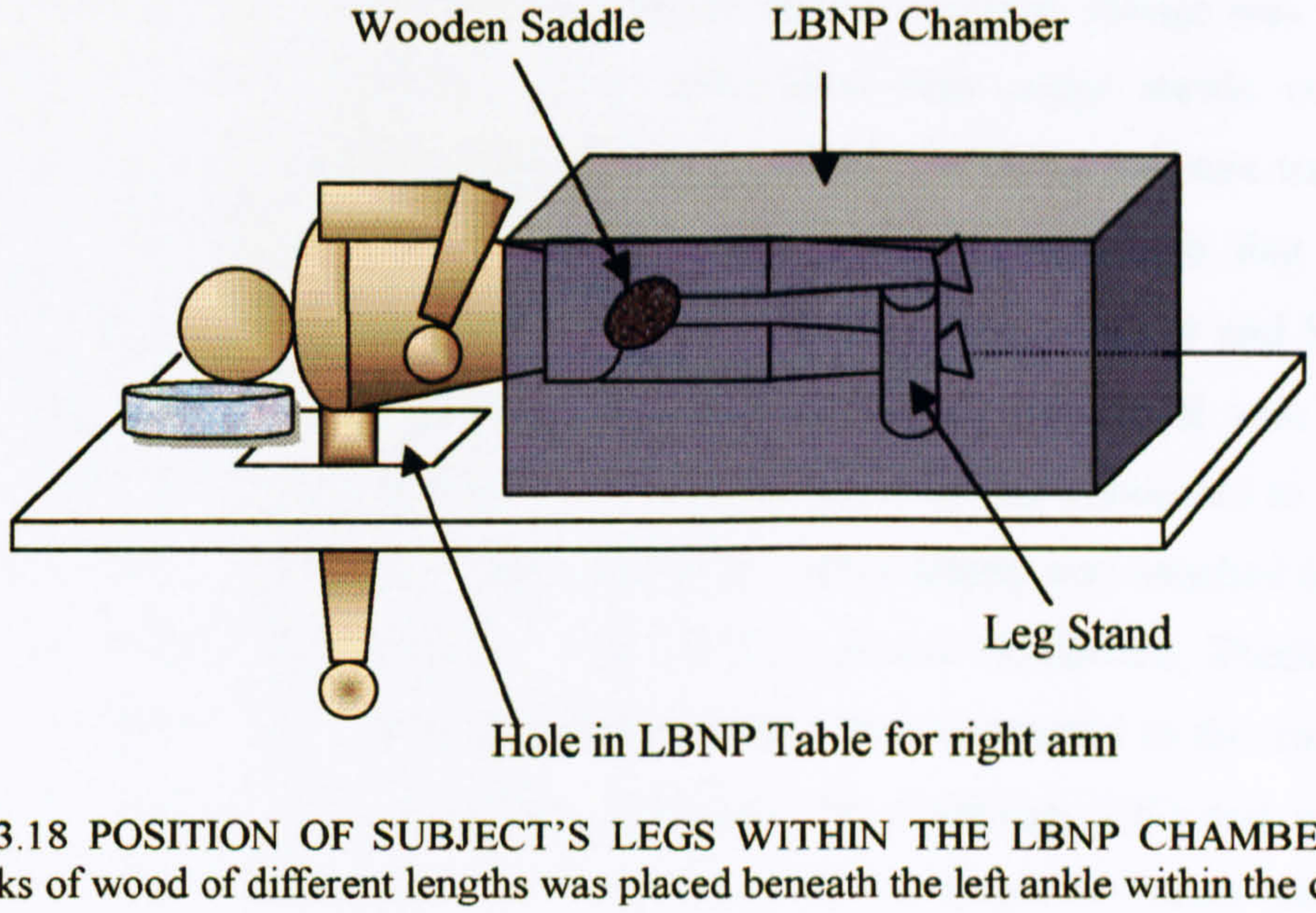


FIGURE 3.18 POSITION OF SUBJECT'S LEGS WITHIN THE LBNP CHAMBER. One of three blocks of wood of different lengths was placed beneath the left ankle within the chamber to support the upper leg.

The pressure in the chamber was reduced by means of a vacuum pump. Chamber pressure was monitored by means of a water manometer (full scale deflection ≡ 25 mmHg) and recorded using a pressure transducer and a Maclab 4/e and Performa 5200 computer

(Macintosh, Apple Computers Inc, Cupertino, USA). Table 3.3 shows an example of the order of LBNP used and shows the number and timing of blood flow measurements.

Activity	Forearm Blood Flows	Chamber Pressure (mmHg)	Duration (min)
Baseline at rest	0	0	20
Baseline measures	8	0	3
Recovery	0	0	3
First LBNP	8	-10	$3^1/_2$
Recovery	0	0	3
Second LBNP	8	-15	$3^1/_2$
Recovery	0	0	3
Third LBNP	8	-5	$3^1/_2$
Recovery	0	0	3
Fourth LBNP	8	-20	$3^1/_2$
Recovery	0	0	3
Baseline measures	8	0	3

TABLE 3.3 EXAMPLE OF A TYPICAL CARDIOPULMONARY BARORECEPTOR FUNCTION ASSESSMENT PROTOCOL

LBNP = Lower body negative pressure. The chamber pressures listed above are a typical example of the order used. The order of pressures used was randomised between subjects.

Central venous pressure measurement. Central venous pressure change was monitored by means of a catheter introduced into an antecubital vein under sterile conditions and connected by a Luer lock tap and Portex tubing system to a sterile pressure transducer. The procedure entailed the arm being placed in a dependent position so that there was a continuous column of blood from the catheter to the right atrium (Gauer and Sieker, 1956). A sterile 21-gauge cannula (Vasculon) was inserted into an antecubital vein whilst a cuff around the upper arm was inflated to 40 mmHg. A Luer-lock tap connected to a 60 mm (for female subjects) or 150 mm (for males) length of Portex tubing was attached to the cannula (Fig 3.19). A 1l bag of 0.9% sterile saline (B1324, Baxter Healthcare, Thetford) to which 10,000 international units of heparin had been added, was connected to the transducer via a priming set (K39/Bart, Kimal Scientific Products Ltd, Uxbridge, UK) and two Luer-lock taps. The pressure transducer was connected by a second length of Portex tubing to one of the Luer taps. Fig 3.19 illustrates the apparatus used.

Heparinised saline was periodically flushed through the transducer, tubing and cannula to maintain patency of the system. The pressure transducer could also be turned to ambient to record a 'zero' pressure. Prior to measurement the system was flushed through to

remove gas bubbles and filled with the saline solution so as to provide a continuous column of fluid between the transducer and subject's arm. The transducer was placed close to subject heart level. The vertical height between the transducer and the xiphoid process was measured to permit correction of the pressure measurements to this level. Central venous pressure was monitored and recorded throughout the procedure. The cannula was withdrawn after all experimental procedures were complete, normally after 40 to 50 min.

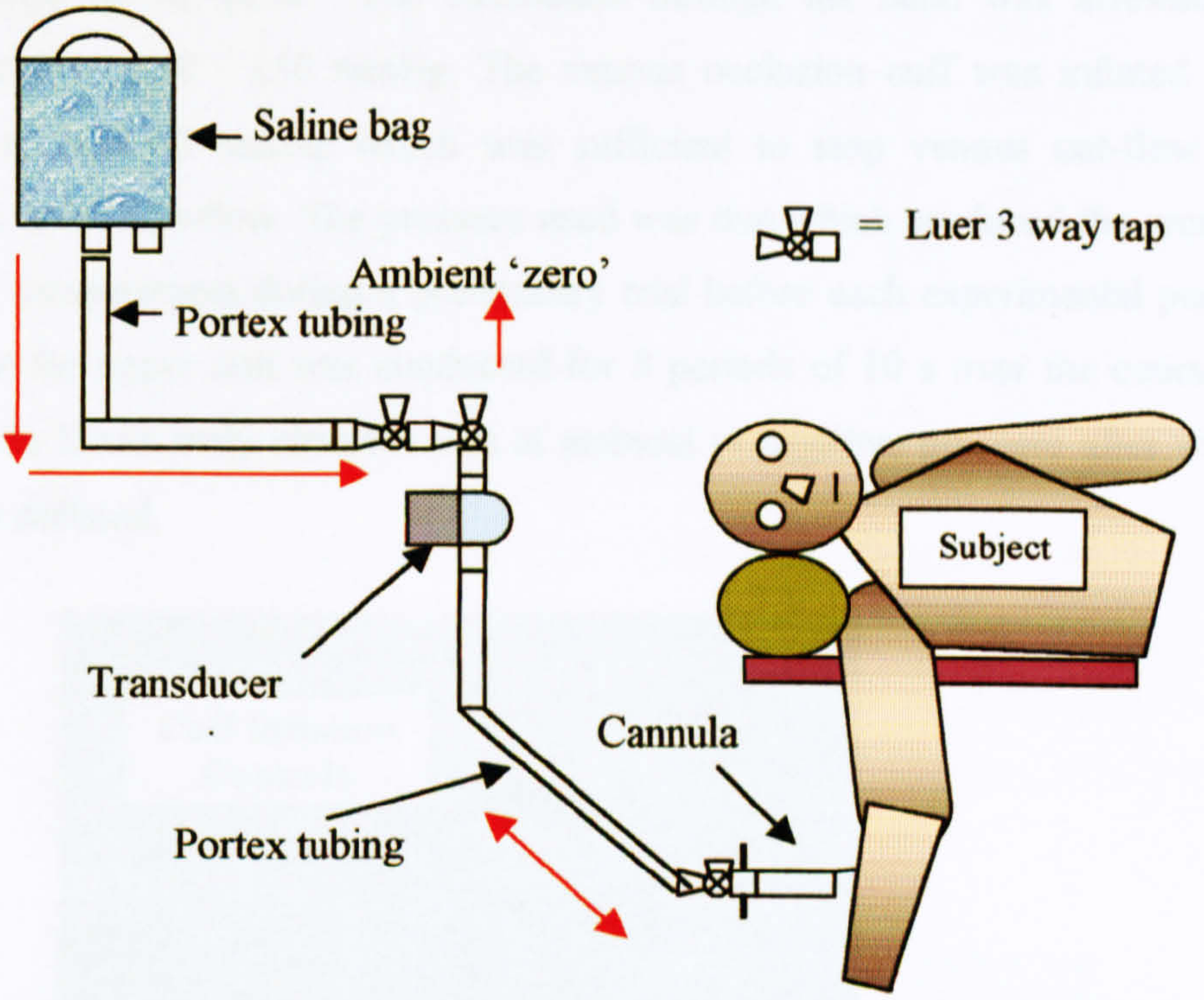


FIGURE 3.19 APPARATUS FOR CENTRAL VENOUS PRESSURE MEASUREMENT. A sterile 21-gauge cannula was inserted into an antecubital vein. A Luer-lock tap connected to Portex tubing was attached to the cannula. A 1l bag of 0.9% saline containing 10,000 IU heparin was connected to the transducer via a priming set and two Luer-lock taps. The pressure transducer was connected by a second length of Portex tubing to one of the Luer taps.

Finapres. Arterial pressure was measured non-invasively by means of the Penàz principle (Penàz, 1973) using a Finapres digital arterial pressure measurement system. The apparatus consisted of a finger cuff placed around the ring finger of the right hand, an electropneumatic servo-system in a box secured about the wrist and the main control and monitoring unit to which these are attached by a pressure and control line. Arterial pressure was measured with the subject at rest before insertion of the cannula. Finapres was not employed during the main experimental period because arterial flow to the hand was occluded during forearm blood flow measurement. Finapres values were corrected according to the vertical distance between finger cuff and the xiphoid process.

Venous Occlusion Plethysmography. Forearm blood flow (and thus vascular resistance) was estimated by means of a mercury-in-silastic strain gauge placed around the left forearm (Fig 3.21) to measure changes in forearm circumference during periods of forearm venous occlusion (Whitney, 1953). The arm cuffs were inflated rapidly to preselected pressures and rapidly deflated using an electropneumatic cuff inflation unit (Fig 3.20) which was supplied with air at a pressure of 50 $lbf.in^{-2}$. The circulation through the hand was arrested by inflating the wrist cuff to 140 - 150 mmHg. The venous occlusion cuff was inflated to a pressure between 40 and 60 mmHg which was sufficient to stop venous out-flow but insufficient to affect arterial in-flow. The pressure used was that which produced the greatest forearm blood flow measurement during a preliminary trial before each experimental period. Venous occlusion at the upper arm was conducted for 8 periods of 10 s over the course of the 3½ min whilst the lower body chamber was at ambient or negative pressure after which both arm cuffs were deflated.

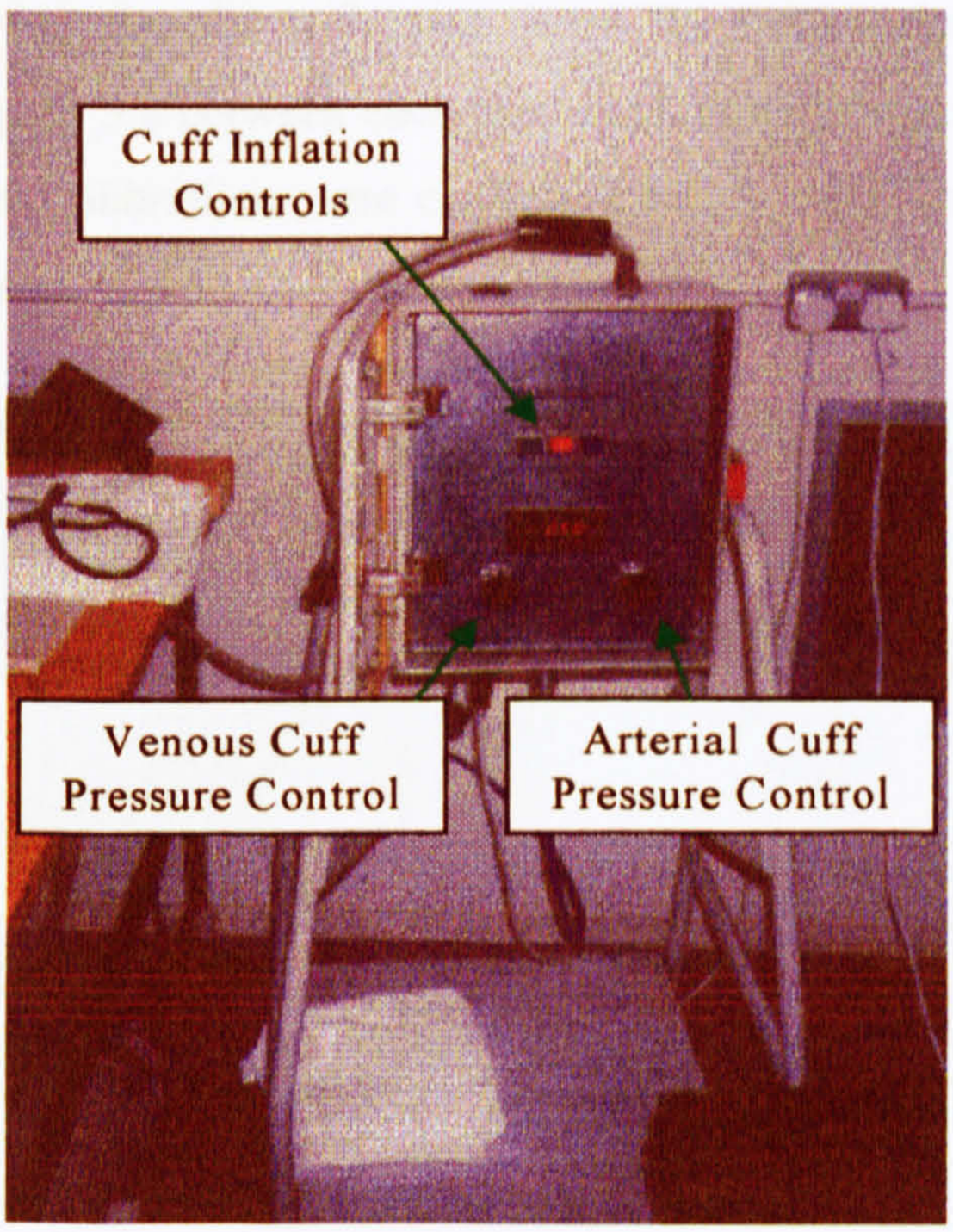


FIGURE 3.20 CUFF INFLATION UNIT. The cuff pressure for venous occlusion was set between 40 and 60 mmHg. The pressure used was that which produced the greatest forearm blood flows during preliminary measures. Arterial occlusion pressure was set at 140 - 150 mmHg.

Fig 3.21 shows a mercury-in-silastic strain gauge attached to a subject's forearm. Three lengths of gauge were used (255, 275 and 295 mm) to allow close fitting for different sized forearms. The gauge was attached at the point of widest circumference and held in place by strips of transpore tape (3M Health Care, Borken, Germany). Talcum powder was sprinkled on the central section of each piece of tape prior to fixation to the skin. The tape when attached to the arm allowed the gauge to move freely around the arm (as the forearm expanded) but not along. The arm was supported at the elbow and wrist at heart level.

Change in the resistance of the 'mercury in silastic' strain gauge was recorded using a Wheatstone bridge circuit and amplifier. The gauge was connected to the Maclab 4/e processor via an amplifier. Gauge resistance was converted to a mV output by the amplifier and recorded on the computer hard drive. Between each measurement the gauge was held in a retort stand with a 25 g weight suspended from it. Prior to each measurement the gauge output with the 25g weight was zeroed to provide a baseline. On attachment to the arm the gauge was tightened or loosened until the baseline output was reacquired. Strain gauge calibration consisted of turning the calibration screw three times clockwise and three times anti-clockwise, pausing for 3 s between each turn. Each turn of the screw changed the length of the gauge by 0.4mm. Calibrations were conducted before and after each series of forearm blood flow measurements.

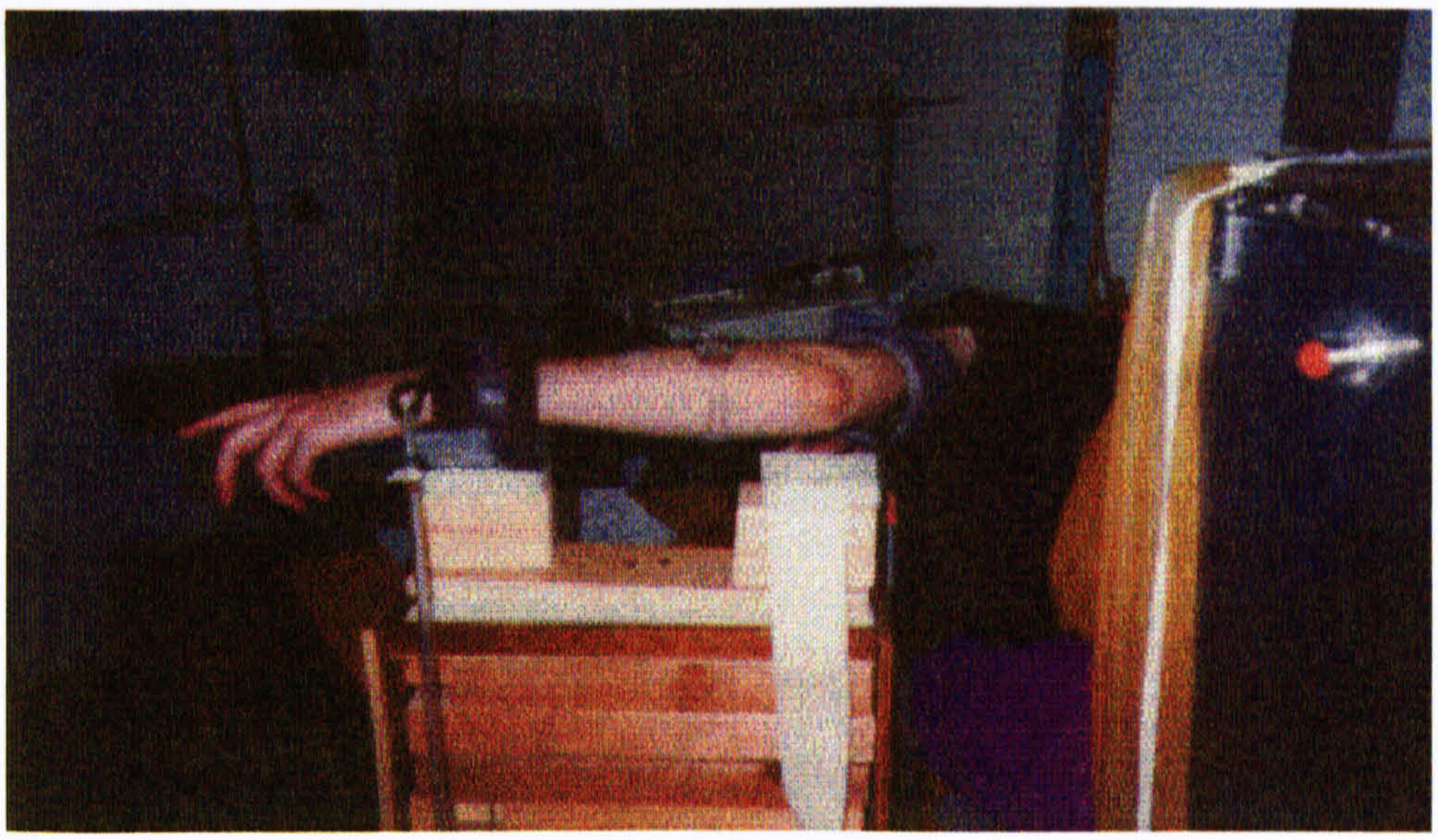


FIGURE 3.21 FOREARM STRAIN GAUGE PLETHYSMOGRAPHY. The strain gauge was placed around the widest circumference of the forearm. Talcum powder was sprinkled on the central section of each piece of tape prior to fixation to the skin. The tape when attached to the arm allowed the gauge to move freely around the arm, but not along.

Forearm blood flows were calculated by plotting the change in μV deflection against time for the linear portion of the flow recording as shown in Figure 3.22.

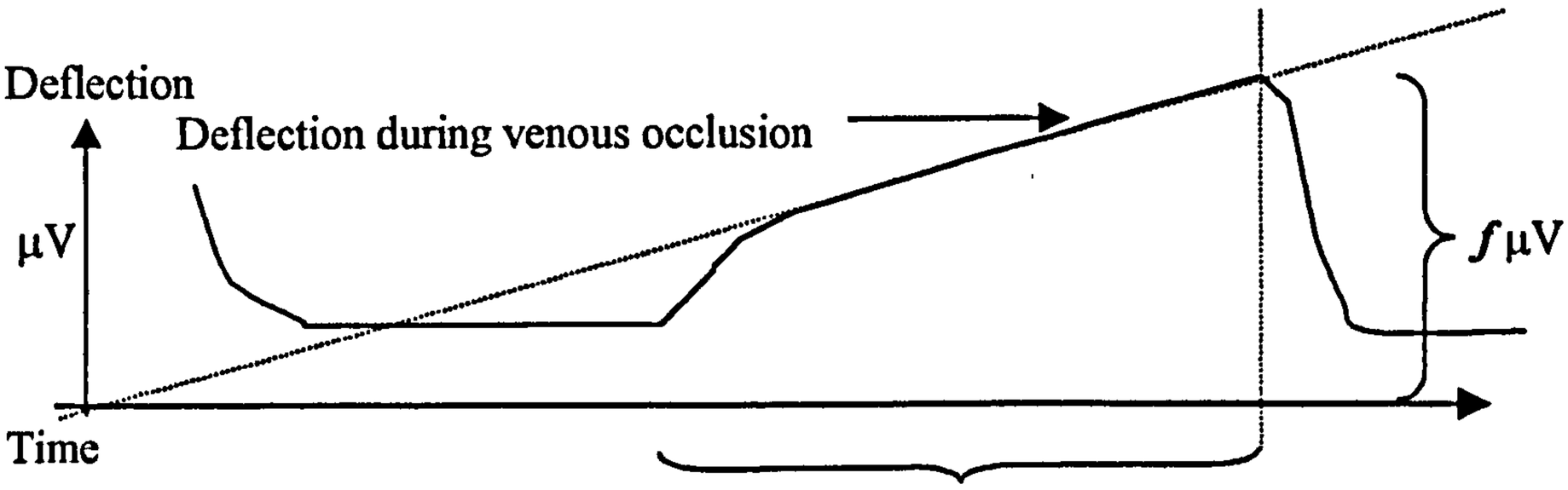


FIGURE 3.22 FOREARM BLOOD FLOW CALCULATION

Blood Flow Calculation:

- Circumference of strain gauge = x mm
- One turn of strain gauge calibration knob ≡ y mm change in circumference.
- Typical calibration of 3 turns = $3y$ mm = d μV deflection.
- $\therefore$ Calibration = $\frac{3y}{x}$ x 100 = % Δ Circumference

  and as % Δ Circumference x 2 = v % Δ Volume

  $$\left[\frac{3y}{x} \times 100\right] \times 2 = v\ \%\ \Delta\ \text{Volume}$$

- if $3y$ mm ≡ d μV ≡ v %
- then 1 μV ≡ $\frac{v}{d}$
- If the mean slope for 8 forearm blood flow (FBF) measurements (i.e. change in strain gauge length over the t s duration of venous occlusion), is $\frac{\int}{t}$ μV.s^{-1} then

- $\frac{f}{t} \times \frac{v}{d} \times 60 = \text{FBF ml.dl}^{-1}.\text{min}^{-1}$.

- Forearm vascular resistance (FVR) is given by:

$$\frac{\text{MAP}}{\text{FBF}} \quad \text{mmHg/ml.dl}^{-1}.\text{min}^{-1} \text{ (PRU)}$$

The mean forearm vascular resistance for each LBNP was plotted against the corresponding value of central venous pressure to provide a measure of cardiopulmonary baroreflex sensitivity (gain of the slope).

3.5.5 ESTIMATION OF ORTHOSTATIC TOLERANCE.

The ability of the subject to tolerate orthostatic stress simulated by progressively increasing LBNP was measured using a progressive, incremental LBNP stress test (Convertino, 1993; Watenpaugh et al., 1994). The assessment required that the subject be exposed to incremental LBNP until signs or symptoms of pre-syncope occurred.

Procedure. The subject lay at rest within the LBNP chamber at ambient pressure for approx 20 min (Fig 3.23). The pressure within the LBNP chamber was then reduced from ambient by 10 mmHg every 3 min. The subject was instructed to relax all muscles and only speak if he/she felt any symptoms or wished to stop for any reason. One experimenter monitored the subject ensuring that he/she did not fall asleep and watched for signs of pre-syncope. A second experimenter (a physician) monitored the arterial pressure and electrocardiogram for signs of pre-syncope. Arterial pressure was measured throughout by means of a Finapres, as previously described (Penàz, 1973) and electrical activity of the heart by means of lead II of a 3 lead electrocardiogram. The objective was to determine the level of suction and the duration of the exposure to LBNP endured before signs and symptoms of pre-syncope occurred. As soon as pre-syncope occurred LBNP was stopped by disconnecting the box from the vacuum source. Subject recovery was always immediate and was monitored until baseline measures were regained.

FIGURE 3.23 APPARATUS FOR THE ASSESSMENT OF TOLERANCE TO LBNP. The subject lay in the lateral decubitus position with Finapres attached to a finger of the right hand. Cushions were placed under the body and head for comfort and to minimise the desire for the subject to move.

The point of pre-syncope provided a quantitative measure of the subject's tolerance to a simulation of orthostatic stress. This measure was derived from the sum of the products of each level of suction (mmHg) and the time (min) for which the subject was exposed i.e. {(Stage1 pressure x duration) + (Stage2 pressure x duration) + …}. This measure is termed the Cumulative Stress Index (CSI, units = mmHg x min) (Levine et al., 1991; Stevens et al., 1992).

Cessation criteria and signs of pre-syncope. The risk of vaso-vagal syncope existed should lower body negative pressure have been continued beyond the first signs and/or symptoms of pre-syncope. Should such a faint have occurred the subject would have recovered immediately on cessation of suction. The primary signs of impending syncope are a precipitous drop in arterial pressure concomitant with or immediately followed by a decreasing heart rate. The criteria for terminating the exposure to LBNP were:

- Asystole
- R-R interval in excess of 2 s.
- Elongation of the P-R interval beyond 0.25 s.
- Sudden precipitous decrease in systolic pressure > 25 mmHg in 1 min
- Sudden precipitous decrease in diastolic pressure > 15 mmHg in 1 min
- Sudden precipitous decrease in heart rate > 15 bpm/min
- A systolic pressure < 80 mmHg
- Nausea, dizziness, pallor, sweating.
- Impaired consciousness
- The subject requested that the procedure to be stopped.

3.6 PARABOLIC FLIGHT EXPERIMENTS – INTEGRATED BAROREFLEX FUNCTION.

The physiological responses to Valsalva's manoeuvre performed before, during and after microgravity were determined to examine the effects of microgravity on integrated baroreflex function. A proposal to undertake this assessment during exposure to microgravity was submitted to the European Space Agency Parabolic Flight Directorate. The acceptance of the proposal heralded a validation period prior to the flights in which apparatus was produced and during which the subjects were trained in the use of associated equipment and procedures.

The parabolic flights were performed in a specially modified European Space Agency Airbus A300 aircraft (Fig 3.24). The parabolic flight profile comprised 33 - 34 parabolas, each separated from the next by an interval of 3 - 7 min, over a period of approximately $1^1/_2$ hr. Each parabola comprised of a pull-up stage as altitude was gained imposing $+1.8G_Z$ on the aircraft and occupants for approximately 20 s. At about 29,000 ft the Airbus flight path was levelled off and a powered dive was started putting all occupants in to a state of 'free-fall' within the aircraft, producing 20 – 24 s of microgravity. After losing 5000 ft of altitude the dive was terminated by the pilots pulling up into level flight once again, during which time a second 20 s period of aircraft $+1.8G_Z$ was experienced (Fig 3.25).

FIGURE 3.24 AIRBUS 'ZERO-G' A300 IN FLIGHT

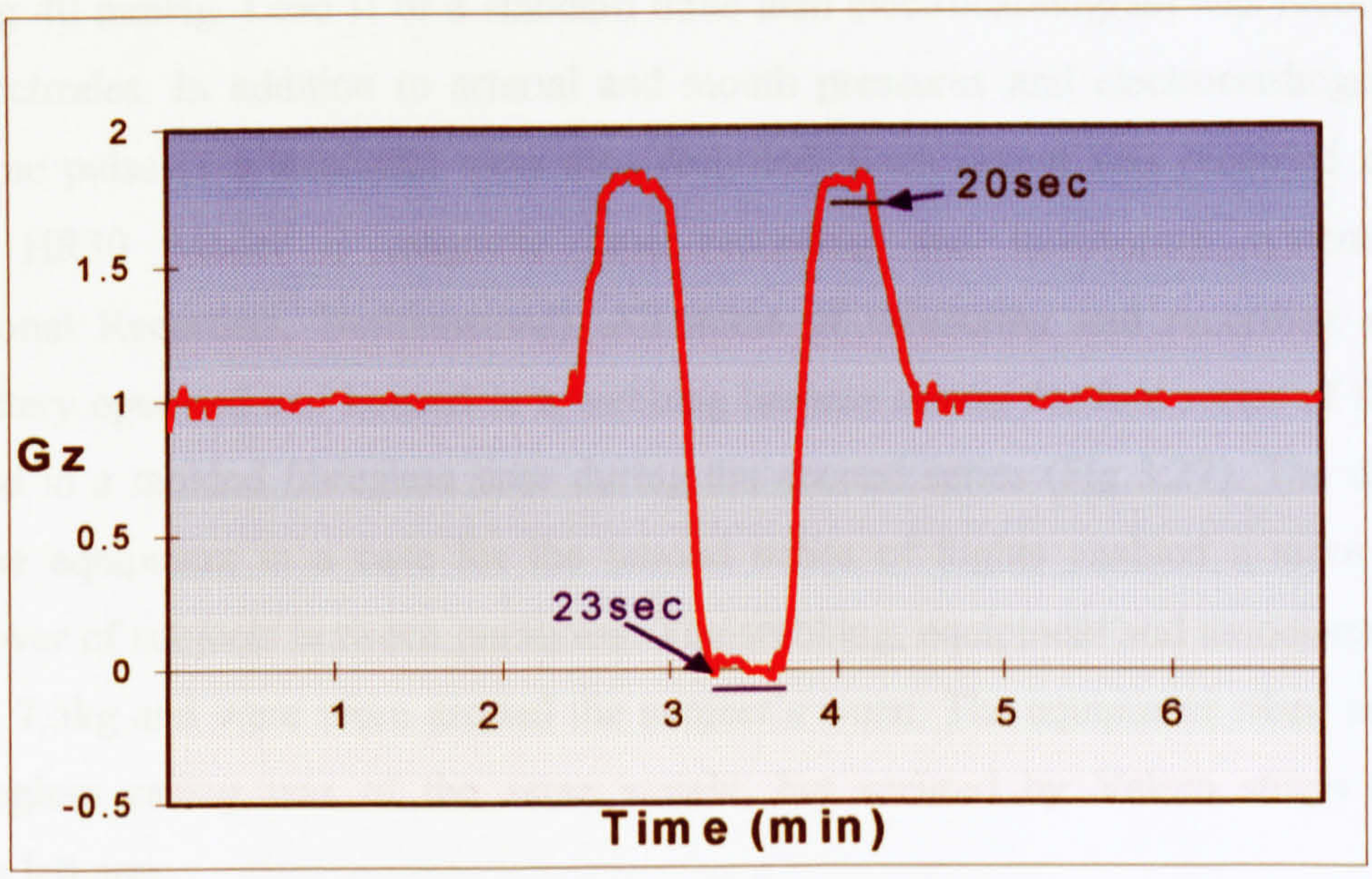


FIGURE 3.25. AIRCRAFT PARABOLA ACCELERATION PROFILE. During each parabola the aircraft was subjected to a 20 s period of $+1.8G_Z$ preceding and succeeding a 20 – 24 s period of microgravity. Occupants of the aircraft in the prone or supine position experienced this transverse hypergravity along the antero-posterior axis.

The apparatus and procedure developed during validation work enabled a 10 s Valsalva's manoeuvre at 40 mmHg expiratory effort to be performed and the response measured within 25 s. This enabled 5 - 8 measures of baroreflex function to be obtained during the course of one flight for each subject. Comparisons between the responses measured during microgravity and those measured at +1G were made in order to investigate whether an acute exposure to microgravity altered the integrated baroreflex response and whether this response was different to that measured at +1G in the seated position or during 6° head-down tilt. The record forms used and outlines of in-flight and post-flights schedules are presented in Appendix K.

Apparatus. Digital arterial pressure was measured by means of a TNO Mod 2 Portapres system (TNO Biomedical Instrumentation Research Unit) based on the Penaz principle (Penaz, 1973)(Appendix L). A Portapres finger cuff of appropriate size was placed on the ring finger of the left hand. Mouth pressure was recorded by means of a pressure transducer (CELESCO LSVR ± 100 mmHg) and amplifier, the output of which was displayed on a 16 crystal LED display calibrated to indicate 1 mmHg pressure per LED, with the central LED

indicating 40 mmHg. Lead II of a standard three lead electrocardiogram was recorded using chest electrodes. In addition to arterial and mouth pressures and electrocardiogram, voice and a time pulse (1 s intervals) were also recorded. Each output was recorded using a 7-channel HR30 Model E magnetic tape recording and monitoring system (TEAC, International Recorders, Berkamstead). All items of measuring and recording equipment were battery operated and housed in a webbing harness during the first series of flights (Fig 3.26) and in a molded fibreglass case during the second series (Fig 3.27). The decision to house the equipment in a case for the second series of flights enabled a more rapid the change over of subjects between parabolas. The webbing, equipment and associated batteries weighed 7.5kg and were worn around the subject's waist. The equipment when enclosed in the fibreglass casing was of the same weight, but secured by Velcro straps under the subject's left arm.

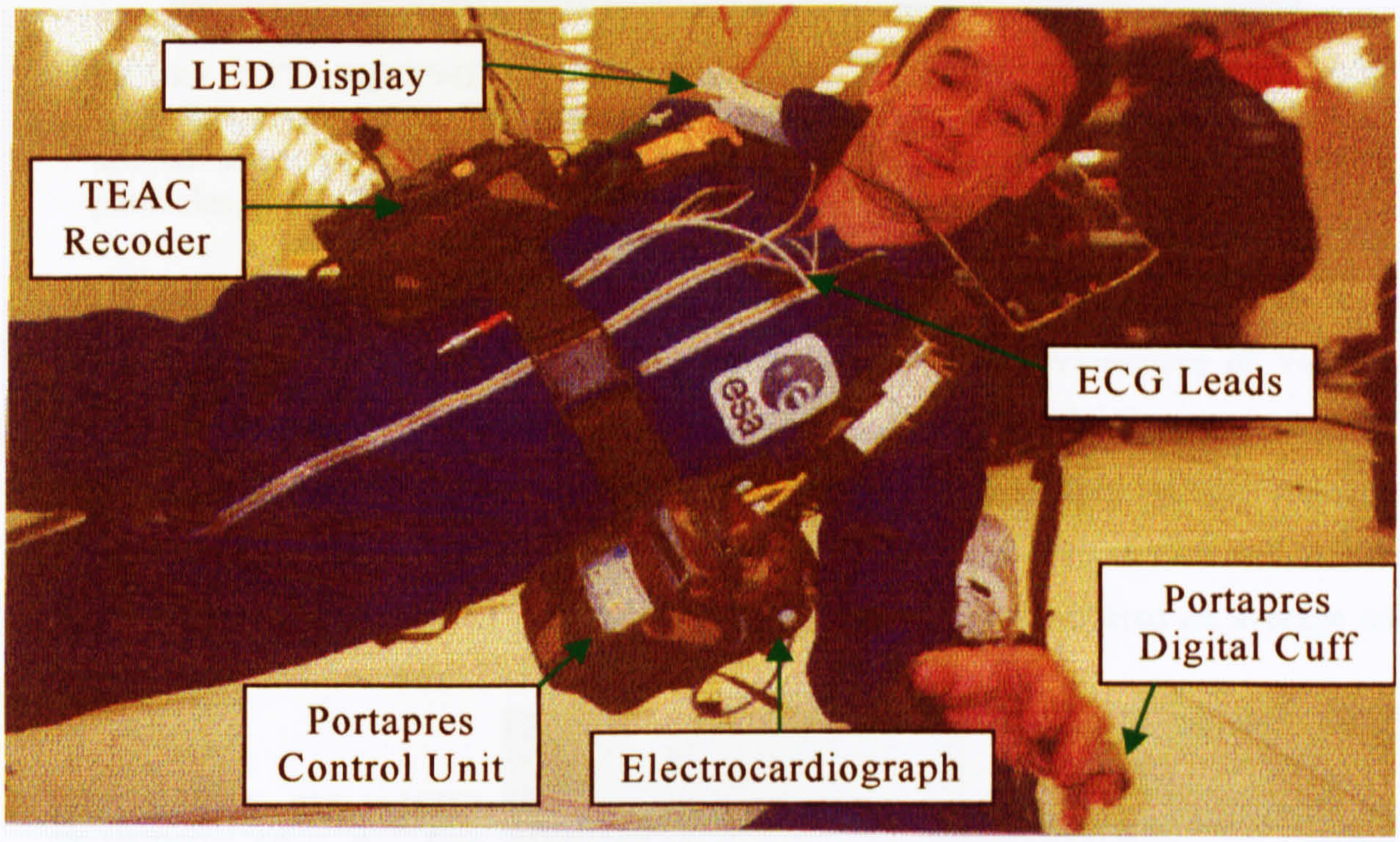


FIGURE 3.26. EQUIPMENT CONFIGURATION FOR THE FIRST SERIES OF PARABOLIC FLIGHTS. The webbing system used to house the recording and monitoring equipment was worn around the subject's upper body to enable him/her to float freely without the hindrence of being attached to the aircraft.

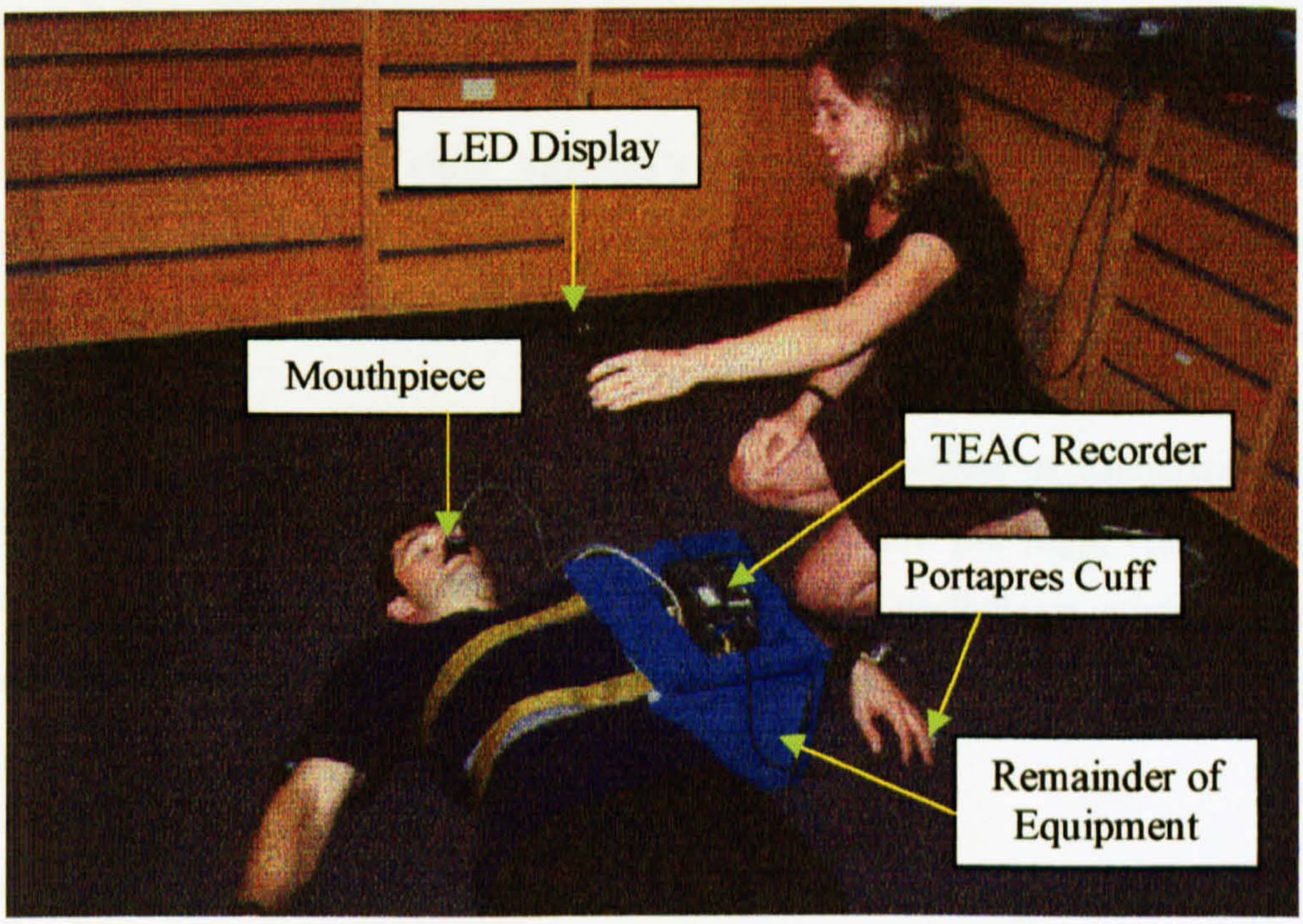


FIGURE 3.27. EQUIPMENT CONFIGURATION FOR THE SECOND SERIES OF PARABOLIC FLIGHTS. The decision to house the equipment in one casing for the second series of flights enabled a more rapid change over of subjects between parabolas.

Pre-flight Training and Procedures: From three weeks before the flight and up to and including the day before take-off, subjects were trained in the performance of Valsalva's manoeuvre in order that complete familiarity with in-flight procedures was attained (Fig 3.28). The in-flight procedures involved the donning and doffing of the associated equipment with sufficient rapidity to allow one subject to change with another within 2 min, thus enabling the exchange of subjects between parabolas which occurred on average once every 3 min.

FIGURE 3.28 PRE-FLIGHT TRAINING. After the first flight, in-flight audio recordings of the pilot's verbal countdowns and preparatory warnings were used for training.

Two hours before take-off three Valsalva's manoeuvres were performed whilst seated with legs outstretched and three Valsalva's manoeuvres whilst at 6° head-down tilt. Each subject performed between five and eight Valsalva's manoeuvres during the course of a flight. Immediately after landing the subject carried out a further three Valsalva's manoeuvres in a seated legs outstretched position and three whilst at 6° head-down tilt.

Anti-motion Sickness Drugs. All subjects took 2 x 15mg tablets of Cinnarizine (Stugeron, Janssen-Cilag Ltd, High Wycombe, UK) three hours before pre-flight baseline Valsalva's manoeuvres as a prophylactic against motion sickness. A preliminary study confirmed that the drug had no effect on the cardiovascular responses to Valsalva's manoeuvre (Appendix Q).

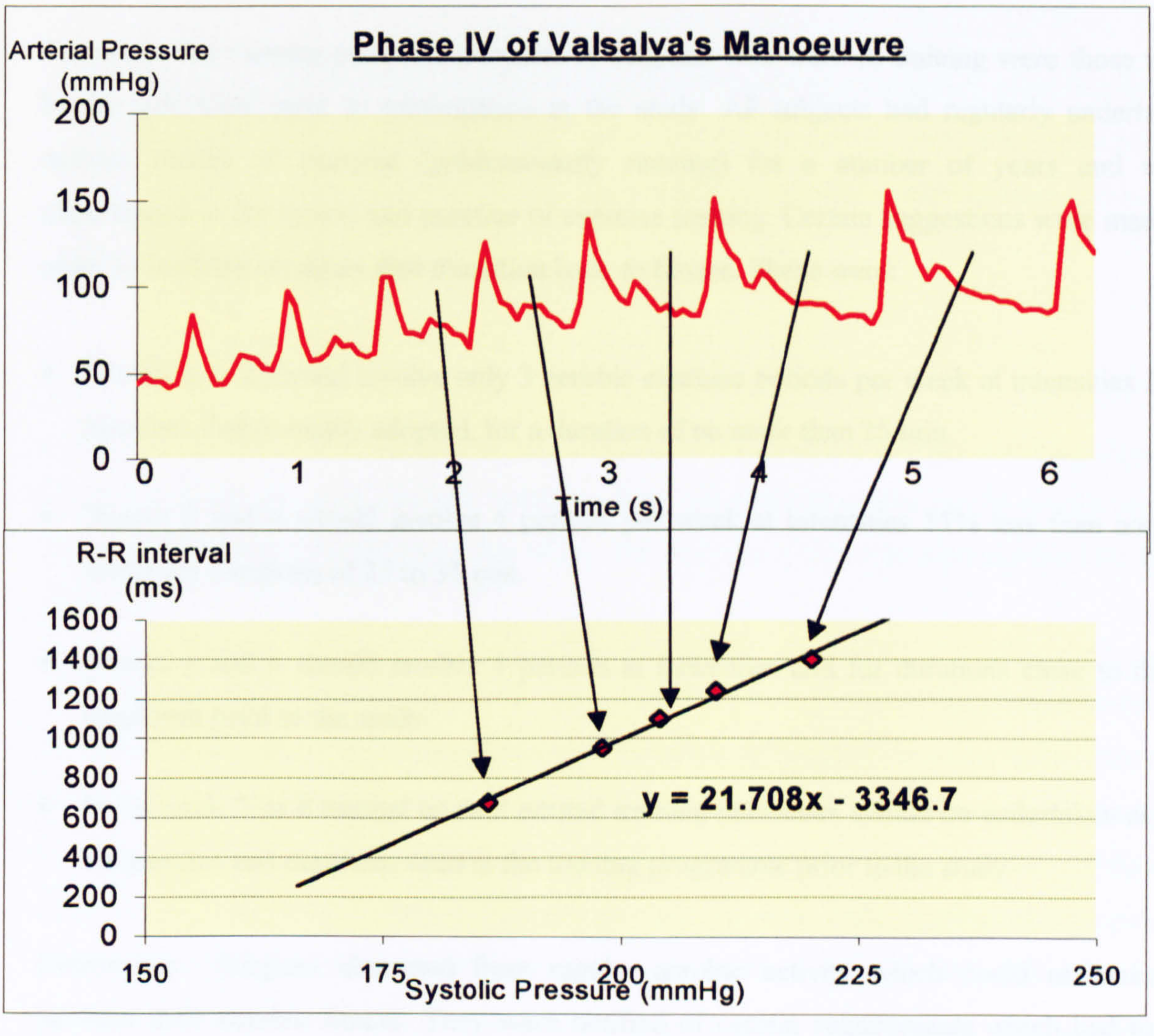
In Flight Procedure. Valsalva's manoeuvres were performed during the microgravity portion of a parabola. Physiological variables were recorded for 10 s before, 10 s during and 10 s after each Valsalva's manoeuvre. The subject was tethered in the supine position throughout whilst two investigators, one either side, controlled the equipment and monitored the outputs (Fig 3.29). At the start of microgravity the subject was given a three second count down to the initiation of the expiratory effort. One of the investigators used a digital watch to count out loud from 10 to 1 at which point the subject ceased expiratory effort. During the Valsalva's manoeuvre the subject was able to monitor mouth pressure by viewing the LED display held by an investigator (Fig 3.29). The end of the microgravity period was indicated by a verbal warning from the pilot and by an acceleration display close to the subject. The point at which $+G_Z$ was reacquired was verbally recorded thus enabling the investigator to know which blood pressure pulses occurred during microgravity and could therefore be used for data analysis, and which occurred during the increasing acceleration of the pull-up. The investigators and subject wore a waterproof procedure sheet attached to the left thigh by Velcro to minimise the possibility of actions being forgotten or mistimed (Appendix M).

FIGURE 3.29 SUBJECT PERFORMING A VALSALVA MANOEUVRE DURING MICROGRAVITY. The configuration of the team was such that the Portapres system was controlled by the investigator on the subject's left and the TEAC recording system controlled by the investigator on the right. Each person was tethered by a system of straps developed to allow horizontal movement but little vertical, and which comprised quick release Velcro fastenings.

Ground based baseline measurements. The subject lay supine at 6° head-down tilt on a bench before each flight and on the same bench (second series of flights) or a sloping knoll of -6° (first series) on the airfield immediately after each flight. The subject rested in this position for approximately 3 min before performing a Valsalva's manoeuvre. The subject performed seated Valsalva's manoeuvres whilst sitting on the floor with legs outstretched to the front. The order of the +1G positions was randomised between subjects but remained the same for a given subject.

Baroreflex Function and Valsalva's Manoeuvre. The Valsalva's manoeuvre consisted of an expiratory effort of 40 mmHg held for 10 s. The expiratory effort was conducted after an unforced maximal inspiration. A small leak in the system (1.95 $l.min^{-1}$) prevented undetected closure of the glottis during the manoeuvre ensuring that the pressure at the mouthpiece reflected that of the alveolar gas. The slope of the R-R interval/systolic pressure relationship obtained from phase IV of the Valsalva's manoeuvre provided was employed as a measure

of baroreflex sensitivity (Palmero et al., 1981). The 'baroreflex sensitivity index', was derived using the pulse intervals immediately following systolic peaks during the arterial pressure response following the cessation of the expiratory effort (see Appendix J). Fig 3.30A shows a typical arterial pressure response to Valsalva's manoeuvre expiratory effort. Fig 3.30B shows the plot of the systolic pressures and associated R to R intervals from the point at which R to R intervals start to increase until the maximum systolic pressure recorded. The slope of the relationship is a measure of the gain of the reflex or baroreceptor sensitivity index.



FIGURES 3.30A & 3.30B ILLUSTRATE THE ARTERIAL PRESSURES AND R-R INTERVALS USED TO DERIVE THE BARORECEPTOR SENSITIVITY INDEX. The systolic pressure associated with the first R-R interval greater than that preceding it was the first arterial pressure measure to be used in the calculation of baroreceptor sensitivity index. Each subsequent systolic pressure and succeeding R-R interval after this up to the last systolic pressure to show a rise was included. The plotting of systolic pressure against R-R interval derived the slope of the relationship used as the measure of sensitivity.

3.7 EXERCISE TRAINING/DETRAINING

During the conditioning period subjects were required to either re-embark upon their normal exercise-training regimen or cease from undertaking regular aerobic exercise. Those subjects who were to retrain had either been injured prior to the study and had fully recovered or had become unfit as a result of lack of training due to work commitments. Those who were to detrain were already at an appropriate level of fitness and were prepared to abide by the detraining requirements.

Training. The training protocols adopted by subjects who were re-training were those used by the individual prior to participation in the study. All subjects had regularly undertaken aerobic modes of exercise (predominantly running) for a number of years and were experienced in the theory and practice of exercise training. Certain suggestions were made in order to facilitate an injury free transition back to fitness. These were:

- Weeks 1 to 2 should involve only 3 aerobic exercise periods per week at intensities 25% less than that normally adopted, for a duration of no more than 25 min.
- Weeks 3 and 4 should involve 4 periods per week at intensities 15% less than normal levels for durations of 25 to 35 min.
- Weeks 5 and 6 should involve 4 periods at intensities and for durations close to those employed prior to the study.
- From week 7 or 8 normal or near normal training intensities should be undertaken at the frequencies and durations used in the training programme prior to the study.

Detraining. Subjects abstained from regular aerobic activity which could maintain or increase their aerobic fitness. They were notified of certain requirements which had to be adhered to during their detraining period. These were:

- Aerobic exercise involving the repetitive use of a large muscle mass (e.g. running, cycling, swimming, rowing) for durations in excess of 5 min must be avoided for the detraining period, with the exception of the following;
    - In order to minimise the possibility of muscle damage and soreness resultant from the study's $\dot{V}O_2max$ assessments and the eventual resumption of training, one session of low intensity aerobic exercise was able to be undertaken every two weeks. The intensity had to be at least 25% less than that usually adopted when training and had to take the form of running or cycling. The session was not allowed to be greater than 25 min in duration.

- Certain forms of anaerobic exercise could be undertaken providing they were maximal or high intensity in nature. Subjects could not undertake the activity more than twice a week (i.e. any combination twice per week). The following anaerobic exercises were allowed:
    - Weight training
    - Sprinting
    - Plyometrics

Anaerobic training was allowed in order to minimise the muscular atrophy resulting from the detraining. Subjects were advised, however, that this allowance was not to enable muscle mass to be increased, in particular that of leg size, but was a means to maintain the lean mass of the legs.

Statistical Analysis. When Sample size was ≤ 7 and where a Guassian distribution could not be assumed, Wilcoxon non-parametric tests of ranked differences for a two-tailed outcome were used to examine differences within group measures. For examination of measures between groups under similar circumstances Mann-Whitney amended Wilcoxon comparisons were used. One-way analyses of variance with Tukey's post-hoc analysis of means were used where a normal distribution could be assumed and $n \geq 8$. Where $n < 8$, a normal distribution could not be assumed and the sizes of the sample group were unequal, χ^2 tests for independent samples were used. Assessments of strength of relationship were conducted using Pearson's Product Moment. A confidence interval of 0.05 was adopted for statistical comparison. All significant differences are therefore at $p < 0.05$ except when indicated otherwise.

4.0 RESULTS.

4.1 OVERVIEW.

Eight test, seven control and two reserve subjects were recruited onto the study. One test and both reserve subjects dropped out immediately prior to the first series of physiological assessments and a second test subject chose to withdraw after the first series of parabolic flights. Two further volunteers were therefore recruited as test subjects for whom the first series of physiological assessments were undertaken after the first flights[12]. Blood volume, $\dot{V}O_2max$, orthostatic tolerance induced by LBNP and carotid sinus and cardiopulmonary baroreflex sensitivities were therefore successfully measured and recorded for 8 test and 7 control subjects. All measures were obtained in the trained and detrained state for the test group. Integrated baroreflex sensitivity (BRSI) for 6 test subjects was successfully measured and recorded at +1G and during microgravity in the trained and detrained states.

Although at the start of the study (or after retraining) all test subjects had a maximum $\dot{V}O_2max$ greater than 50 $ml.kg^{-1}min^{-1}$, one subject achieved a maximum of only 51.7 $ml.kg^{-1}min^{-1}$ when fully trained. Due to his low level of aerobic conditioning the data from this subject was excluded from general analysis, but was included for examinations of relationships. All trained versus detrained comparisons were therefore undertaken using data from 7 test subjects with the exception of BRSI for which only 6 sets of data were available.

The principle findings were as follows:

- Detraining successfully reduced $\dot{V}O_2max$ and blood volume by 15.6% ($p < 0.01$) and 8.1% ($p < 0.01$) respectively.
- Tolerance to progressive LBNP significantly improved by 22.9% ($p < 0.01$) as a result of detraining.
- No difference was observed between the trained and detrained cardiopulmonary baroreflex sensitivities, however, the mean test group cardiopulmonary gain (trained & detrained measures combined) proved significantly less than that of the mean control group (initial & final measures combined).
- Carotid baroreflex sensitivity was significantly reduced after detraining to a level similar to control.

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[12] Which they were unable to participate in.

- Integrated baroreflex sensitivity measured during microgravity was found to be significantly less than that of both +1G means by an average of 39.8% (compared to Seated) and 40.7% (compared to HDT).
- The mean integrated sensitivities for 1G and microgravity conditions were not, however, altered by the detrained state.

Appendix R contains the raw data for all measurements for control and test groups.

4.2 SUBJECTS

Subject Characteristics. The test group were significantly heavier (+1.9kg) when detrained than when trained (Table 4.2). All other physical characteristics were similar between groups and trained state.

	Test Group (Mean ± SD)				Control Group (Mean ± SD)	
	Trained	Follow Up 1	Follow Up 2	Detrained	Initial	Final
Weight, kg	<u>72.01</u>	72.3*	73.2	<u>73.9</u>	69.9	69.5
	± 11.5	± 10.8	± 11.7	± 11.4	± 8.1	± 8.0
Age, yr	27.3				28.7	
	± 3.0				± 3.9	
Height, cm	177.8				171.9	
	± 8.9				± 9.2	
Heart rate at	57.4		60.7		65.1	64.3
rest, bpm	± 12.2		± 14.0		± 8.4	± 10.6
Systolic BP,	116.1		117.6		122.9	121.3
mmHg	± 4.2		± 5.6		± 7.8	± 5.7
Diastolic BP,	75.0		79.4		80.0	82.1
mmHg	± 7.5		± 8.0		± 7.2	± 5.4

TABLE 4.1. CHARACTERISTICS OF SUBJECTS. Age and height were recorded at the start of the study only.
* = Two data missing.
Follow up 1&2 = Intermediate measures during the conditioning period.
<u>Underscore</u> = Significant difference between trained and detrained measures ($p < 0.05$).

4.3 FITNESS RELATED VARIABLES – $\dot{V}O_2MAX$, BLOOD VOLUME AND TOLERANCE TO PROGRESSIVE LOWER BODY NEGATIVE PRESSURE.

The test subjects de/retrained for a mean of 17 wk. Detraining resulted in a 15.6% reduction ($p < 0.01$) of $\dot{V}O_2max$, an 8.1% decrease ($p < 0.01$) in blood volume and a significant 22.9% increase in tolerance to progressive LBNP (Table 4.2). Time to pre-syncope during LBNP increased by a significant 2 min 9 s for the test group in the detrained state. Figure 4.1 illustrates the relative changes in tolerance to LBNP for both subject groups. No significant changes in any variables were noted for the control subjects during the mean control period of 12 wk. The only significant difference between test and control group measures was a significantly greater test group trained $\dot{V}O_2max$.

	$\dot{V}O_2max$ $ml.kg^{-1}min^{-1}$	Blood Volume Litre	Tolerance to PLBNP CSI	Time to Pre-Syncope s
Test Group				
Trained	<u>**63.5**</u> ± 9.9	<u>**5.70**</u> ± 1.0	<u>**785.7**</u> ± 206.7	<u>**1209.9**</u> ± 172.3
Follow up 1	57.2 ± 6.3	5.48 ± 1.0	-	-
Follow up 2	55.6 ± 7.8	5.29 ± 1.0	-	-
Detrained	<u>**53.6**</u> ± 5.9	<u>**5.24**</u> ± 0.9	<u>**966.1**</u> ± 337.9	<u>**1338.7**</u> ± 236.9
Control Group				
Initial	<u>**45.5**</u> ± 8.7	5.28 ± 0.8	747.4 ± 185.7	1201.9 ± 156.9
Final	<u>**44.3**</u> ± 8.9	5.27 ± 0.8	738.9 ± 195.0	1174.9 ± 153.5

TABLE 4.2 MAXIMUM OXYGEN UPTAKE, BLOOD VOLUME AND TOLERANCE TO PROGRESSIVE LOWER BODY NEGATIVE PRESSURE FOR TEST (n = 7) AND CONTROL (n = 7) GROUPS (MEAN ± SE).
<u>Underscore</u> denotes a significant difference ($p < 0.05$) between trained and detrained states.
<u>Double Underscore</u> denotes a significant difference ($p < 0.01$) between control and trained states.
PLBNP = Progressive Lower Body Negative Pressure, CSI = Cumulative Stress Index (min. x mmHg).

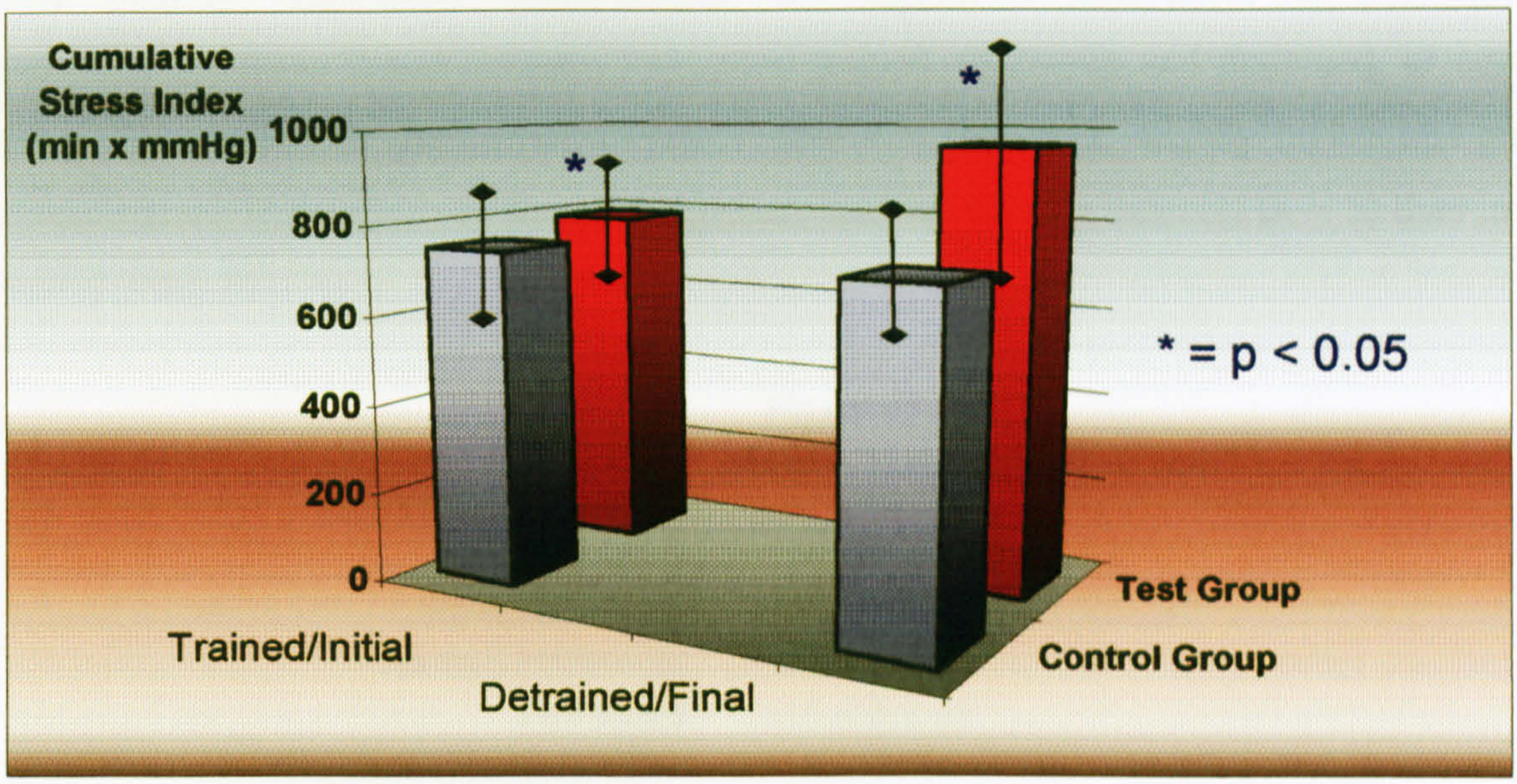


FIGURE 4.1 EFFECT OF TRAINED STATE AND CONTROL PERIOD ON TOLERANCE TO PROGRESSIVE LOWER BODY NEGATIVE PRESSURE (MEAN ± SE).

4.4 MAXIMUM OXYGEN UPTAKE AND BLOOD VOLUME.

The change in $\dot{V}O_2max$ for the control group during the control period varied between 2.4% and 8.4%. Differences between trained and detrained $\dot{V}O_2max$ values for test subjects ranged from 7.2% to 36% (Fig 4.2).

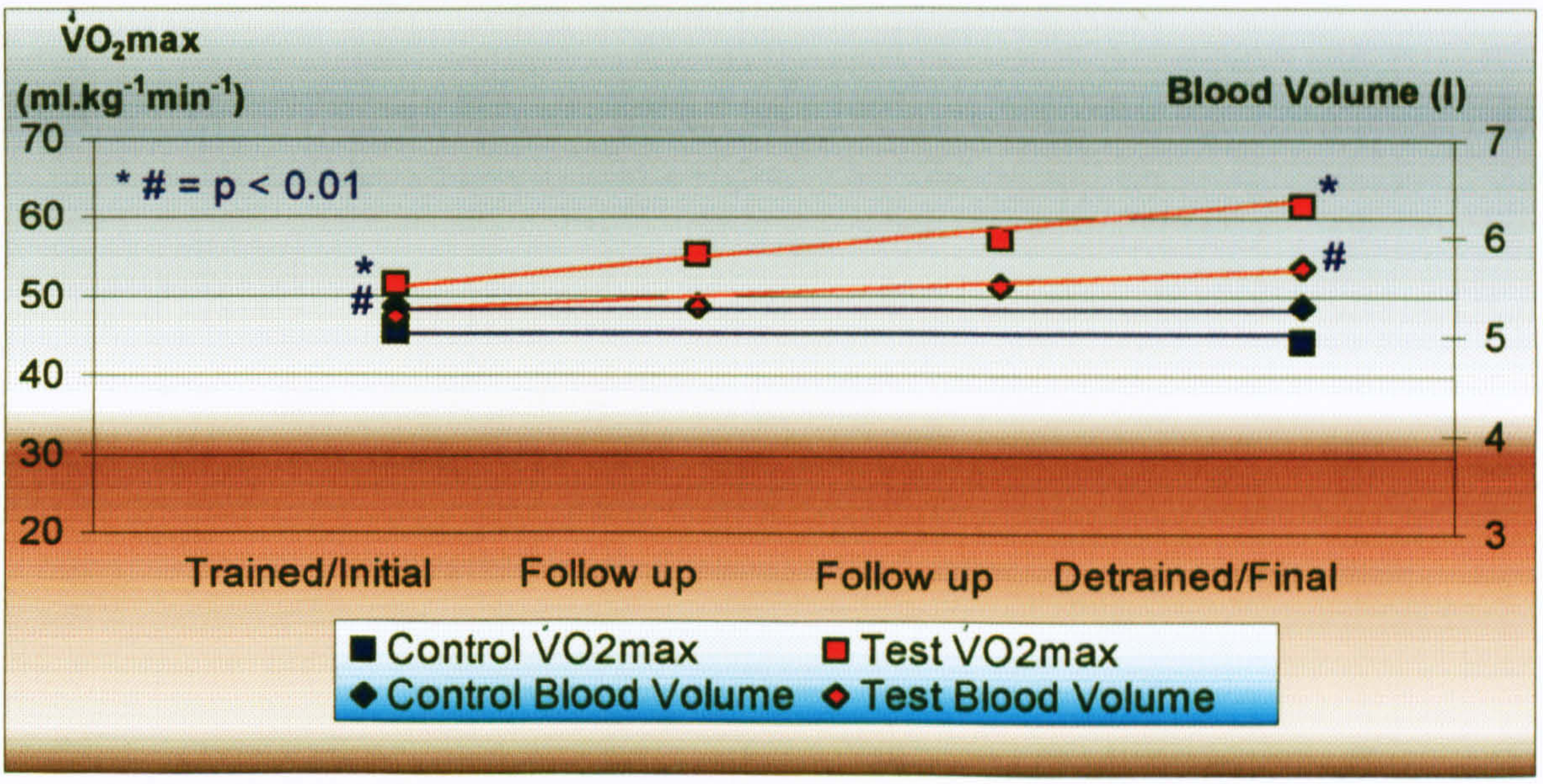


FIGURE 4.2 TEST AND CONTROL GROUP MAXIMUM OXYGEN UPTAKE AND BLOOD VOLUME. Mean test and control group $\dot{V}O_2max$ and blood volume values in relation to each other over the course of the study (n = 7)

4.4.1 BLOOD VOLUME VARIABLES. No significant differences in haemoglobin concentrations were found between test group trained, follow-up and detrained, or control group initial and final baseline conditions (Table 4.3), however, slightly higher test group concentrations were observed due to the greater number of male subjects (n = 5) than in the control group (n = 3).

	Haemoglobin Mean ± SE ($g.dl^{-1}$)
Test Group (n = 7).	
Trained	14.9 ± 1.30
First Follow up	15.6 ± 1.10
Second Follow up	15.7 ± 1.43
Detrained	15.6 ± 2.05
Control Group (n = 7).	
Initial	14.0 ± 2.04
Final	14.1 ± 1.57

TABLE 4.3 HAEMOGLOBIN CONCENTRATIONS RECORDED FOR BLOOD VOLUME MEASUREMENT.

4.5 RESPONSES TO PROGRESSIVE LOWER BODY NEGATIVE PRESSURE.

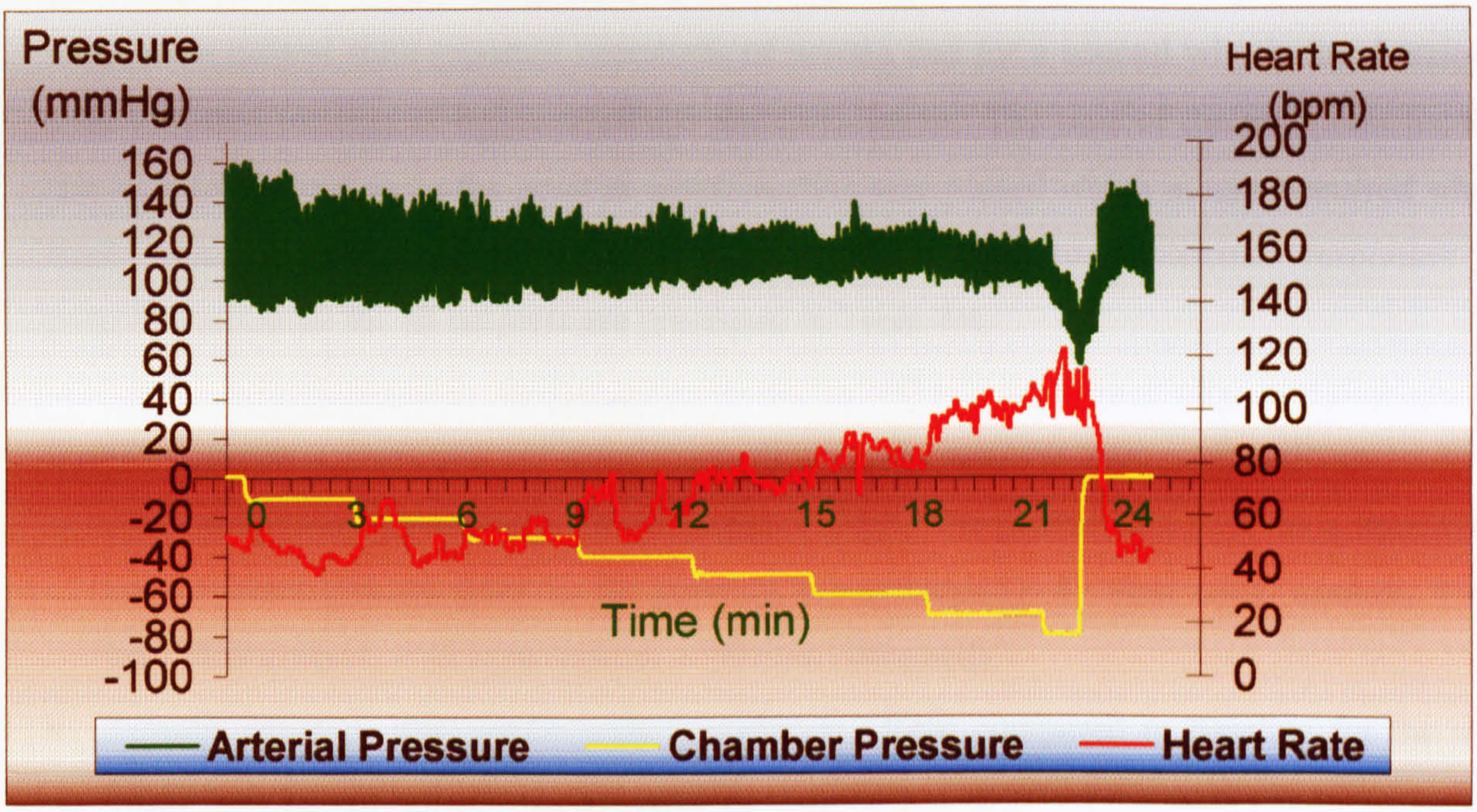


FIGURE 4.3 RESPONSE OF SUBJECT JM TO PROGRESSIVE LOWER BODY NEGATIVE PRESSURE IN THE TRAINED STATE ($\dot{V}O_2max$ = 79.3 $ml.kg^{-1}min^{-1}$)

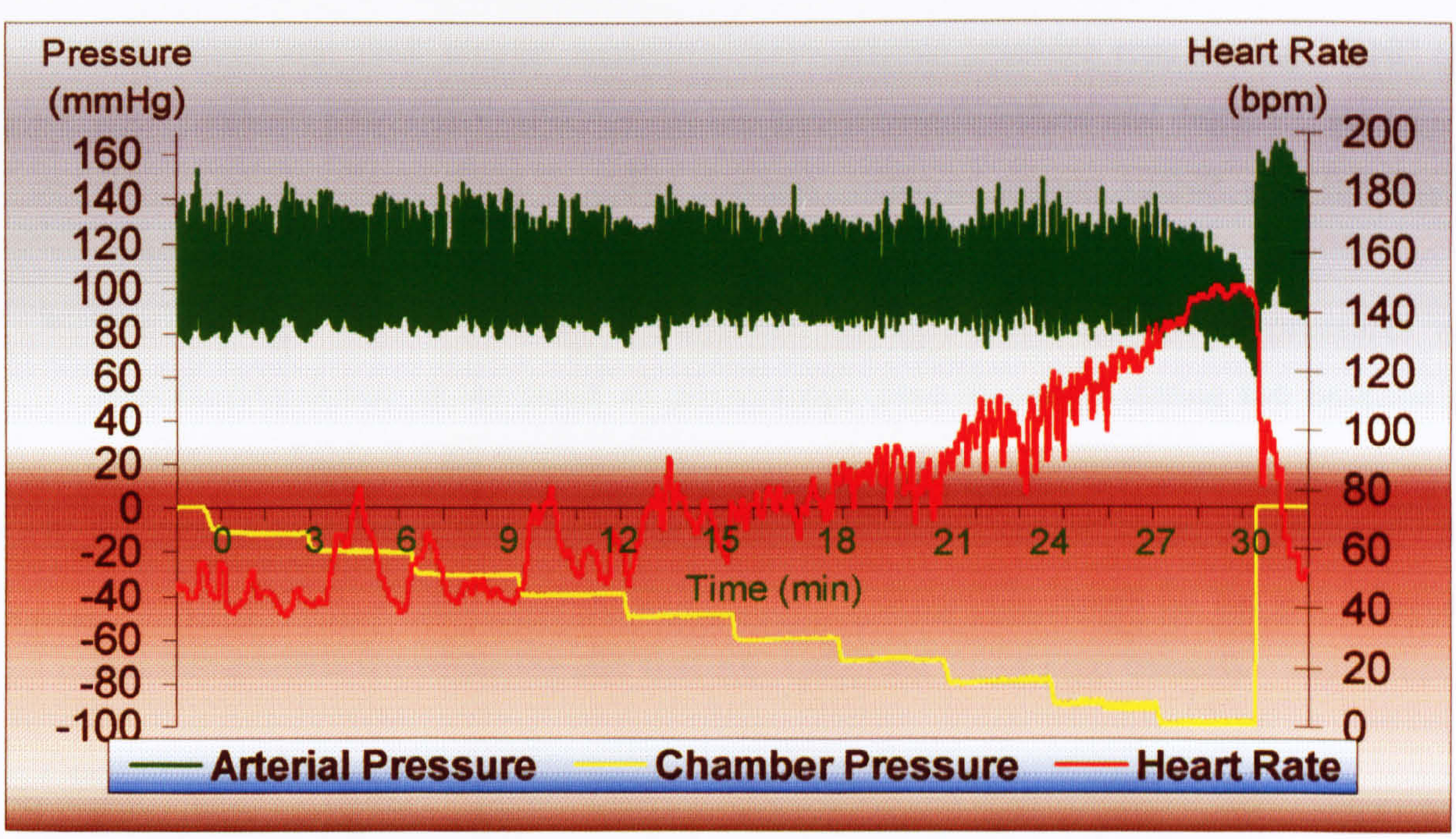


FIGURE 4.4 RESPONSE OF SUBJECT JM TO PROGRESSIVE LOWER BODY NEGATIVE PRESSURE IN THE DETRAINED STATE ($\dot{V}O_2max$ = 62.5 $ml.kg^{-1}min^{-1}$).

Figures 4.3 and 4.4 illustrate the cardiovascular responses of the fittest test subject to progressive LBNP in the trained and detrained state. During LBNP all subjects reached a

point at which either signs or symptoms of impending syncope were noted. On all occasions the end point was recognised by a precipitous drop in arterial pressure except for one subject who in the trained state reported symptoms of nausea and for a second who in the detrained state reported feelings of lightheadedness and detachment. The time of the end-point for the test was considered to be the point at which suction was ceased which in turn occurred when frank signs or symptoms of pre-syncope were noted. The cardiovascular responses to progressive LBNP for all subjects are presented in Table 4.4.

General Trends.

- Heart rate rose significantly for all subjects during the course of LBNP to a maximum level several minutes prior to the point of pre-syncope (+ 47 bpm initial control, + 48 bpm final control, + 32 bpm trained, + 39 bpm detrained).
- Systolic pressure was significantly less during LBNP compared to baseline for the test subjects in the trained state (-10.1 mmHg).
- Diastolic pressure tended to rise during LBNP, significantly in the case of the initial control assessments (+6.5 mmHg).
- For initial and final control measures mean arterial pressure rose during LBNP ($p > 0.05$), but decreased ($p > 0.05$) for the test group in both trained and detrained states.
- The only significant drop in pulse pressure observed during LBNP was for the test subjects in the trained state (-14 mmHg).
- For all subjects pulse pressure and systolic, diastolic and mean arterial pressures were significantly lower at the point of pre-syncope than measured during the baseline rest period (see Table 4.4 for magnitudes).
- Heart rate was significantly higher at pre-syncope than baseline for all subjects (+37 bpm initial control, + 29 bpm final control, + 29 bpm detrained) except for the test subjects in the trained state for whom the rise was not significant (+ 24 bpm trained).

Comparison of Responses to Progressive Lower Body Negative Pressure.

- Comparisons between subject groups showed that the test subjects in the trained state had significantly lower heart rates than the final control subject values during their baseline period (-10 bpm) and during LBNP (-18 bpm).

- Pulse pressure during LBNP for the test subjects in the trained state was also significantly less than that observed during the final measurements for the control group (-9.3 mmHg).

(n = 7)	Control Group (Mean ± SE)		Test Group (Mean ± SE)	
	Initial	**Final**	**Trained**	**Detrained**
Baseline				
Systolic Pressure	130.4 ± 8.3	128.7 ± 9.2	125.7 ± 19.6	132.3 ± 10.8
Diastolic Pressure	78.6 ± 5.9	80.9 ± 7.1	78.3 ± 13.6	81.7 ± 6.4
Mean Arterial Pressure	96.0 ± 5.6	96.7 ± 6.7	94.0 ± 15.2	98.6 ± 6.2
Pulse Pressure	51.9 ± 8.0	47.9 ± 8.9	47.4 ± 8.2	50.6 ± 11.8
Heart Rate	61.1 ± 5.37	67.7 ± 10.7	57.4 ± 8.44	57.6 ± 9.3
Maximum During LBNP				
Systolic Pressure	127.6 ± 10.4	132.4 ± 15.0	115.6 ± 16.8	127.0 ± 8.7
Diastolic Pressure	85.1 ± 5.7	85.9 ± 6.7	82.6 ± 16.0	85.0 ± 7.0
Mean Arterial Pressure	99.3 ± 5.1	101.4 ± 8.6	92.1 ± 15.8	98.0 ± 8.0
Pulse Pressure	42.7 ± 11.8	46.6 ± 12.0	33.4 ± 7.0	42.9 ± 9.0
Heart Rate	108.1 ± 34.1	115.3 ± 27.5	89.4 ± 13.4	96.4 ± 14.7
Pre-syncope				
Systolic Pressure	88.7 ± 8.2	98.6 ± 14.7	81.9 ± 18.3	86.1 ± 14.6
Diastolic Pressure	59.6 ± 14.1	66.0 ± 11.4	52.9 ± 17.9	61.6 ± 11.1
Mean Arterial Pressure	69.4 ± 11.8	76.9 ± 11.7	62.4 ± 17.5	69.7 ± 11.3
Pulse Pressure	29.1 ± 7.6	32.6 ± 10.7	27.6 ± 7.8	24.1 ± 11.2
Heart Rate	97.9 ± 38.8	96.3 ± 31.4	80.9 ± 34.4	86.7 ± 31.2

TABLE 4.4 CARDIOVASCULAR RESPONSES TO PROGRESSIVE LOWER BODY NEGATIVE PRESSURE. All arterial pressures are shown in mmHg and heart rates in beats per minute. Values shown 'During LBNP' were the maximum values attained during the application of LBNP. Values shown at 'Pre-syncope' were the minimum values attained at the point suction was terminated.

Red values indicate significant differences ($p < 0.05$) to baseline values.

Underscore: significant difference ($p < 0.05$) between Maximum LBNP and Baseline values.

Double Underscore: Test subject trained values are significantly different ($p < 0.05$) to Final Control values

4.6 CARDIOPULMONARY BARORECEPTOR SENSITIVITY.

Figure 4.7 presents an example of forearm blood flow measurements during LBNP.

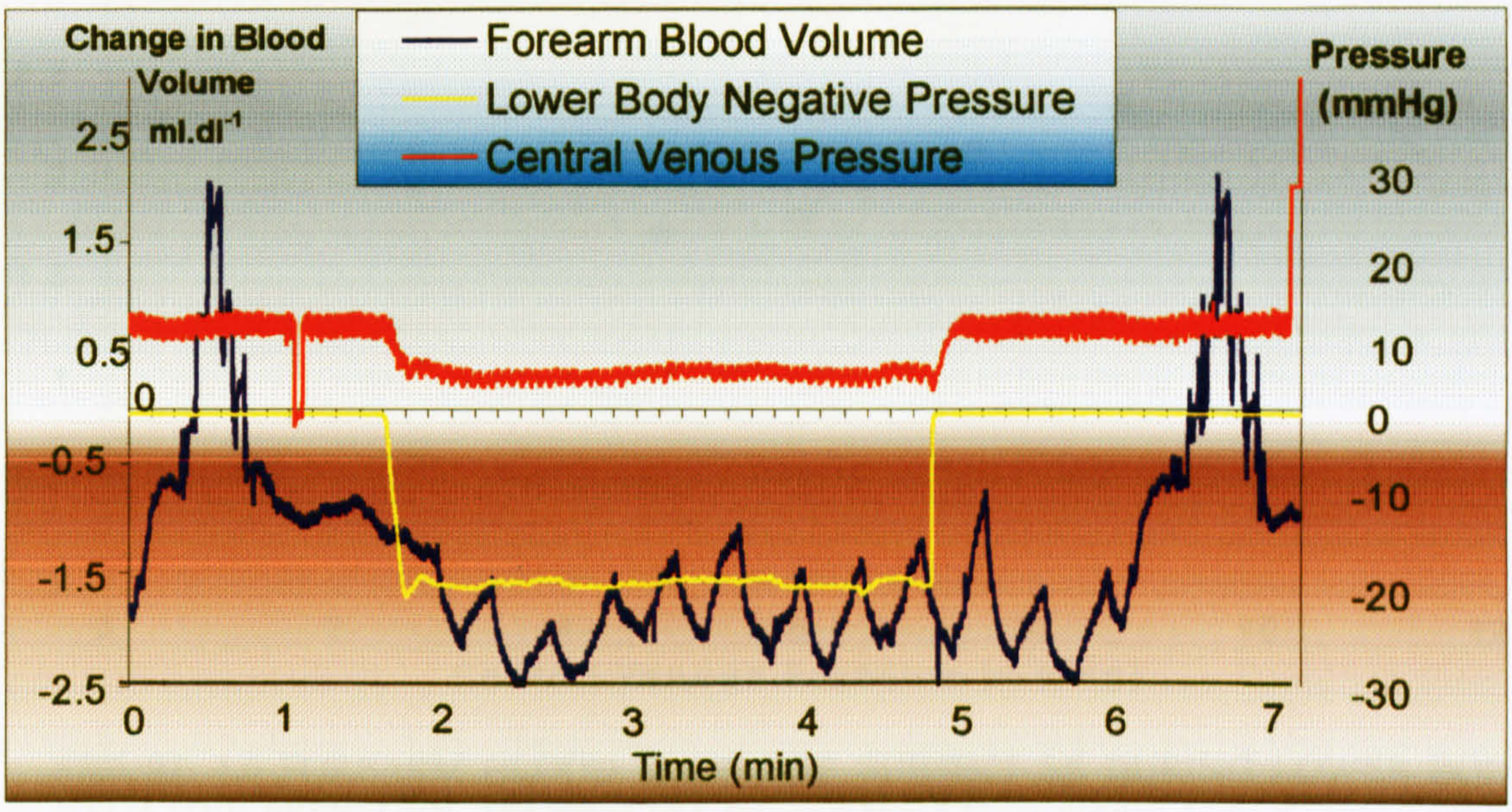


FIGURE 4.5. TYPICAL FOREARM BLOOD FLOW AND CENTRAL VENOUS PRESSURE MEASUREMENTS DURING 15 mmHg LBNP. Eight measurements of forearm blood flow can be seen during LBNP and three on cessation of suction. Forearm strain gauge calibrations can be seen before and after the period of LBNP. A confirmation of transducer 'zero' is shown in the peripheral venous pressure trace prior to LBNP. Venous pressure and LBNP outputs are shown in mmHg.

Forearm blood flow typically decreased with the fall of central venous pressures produced by LBNP (Fig 4.6). Mean forearm vascular resistance was calculated as mean arterial pressure divided by the mean forearm blood flow. A linear relationship was found between the measures of forearm vascular resistance and central venous pressure obtained at the different lower body pressures (Fig 4.7). The slope of this line provided the measure of cardiopulmonary baroreflex sensitivity.

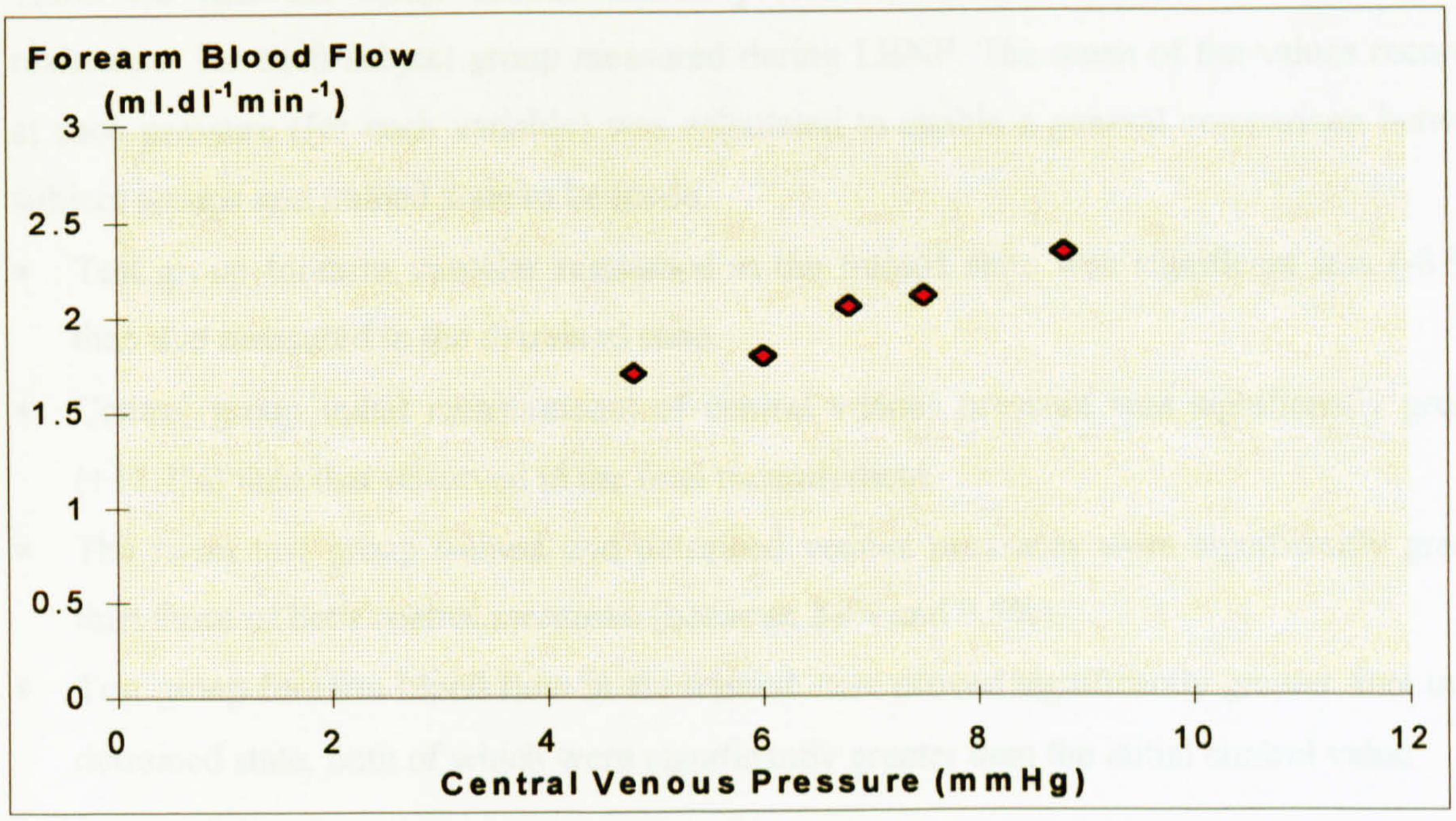


FIGURE 4.6 FOREARM BLOOD FLOW FOR SUBJECT SE DURING LOWER BODY NEGATIVE PRESSURE. The mean of 8 forearm blood flows plotted against central venous pressure for 0, 5, 10, 15 and 20 mmHg LBNP.

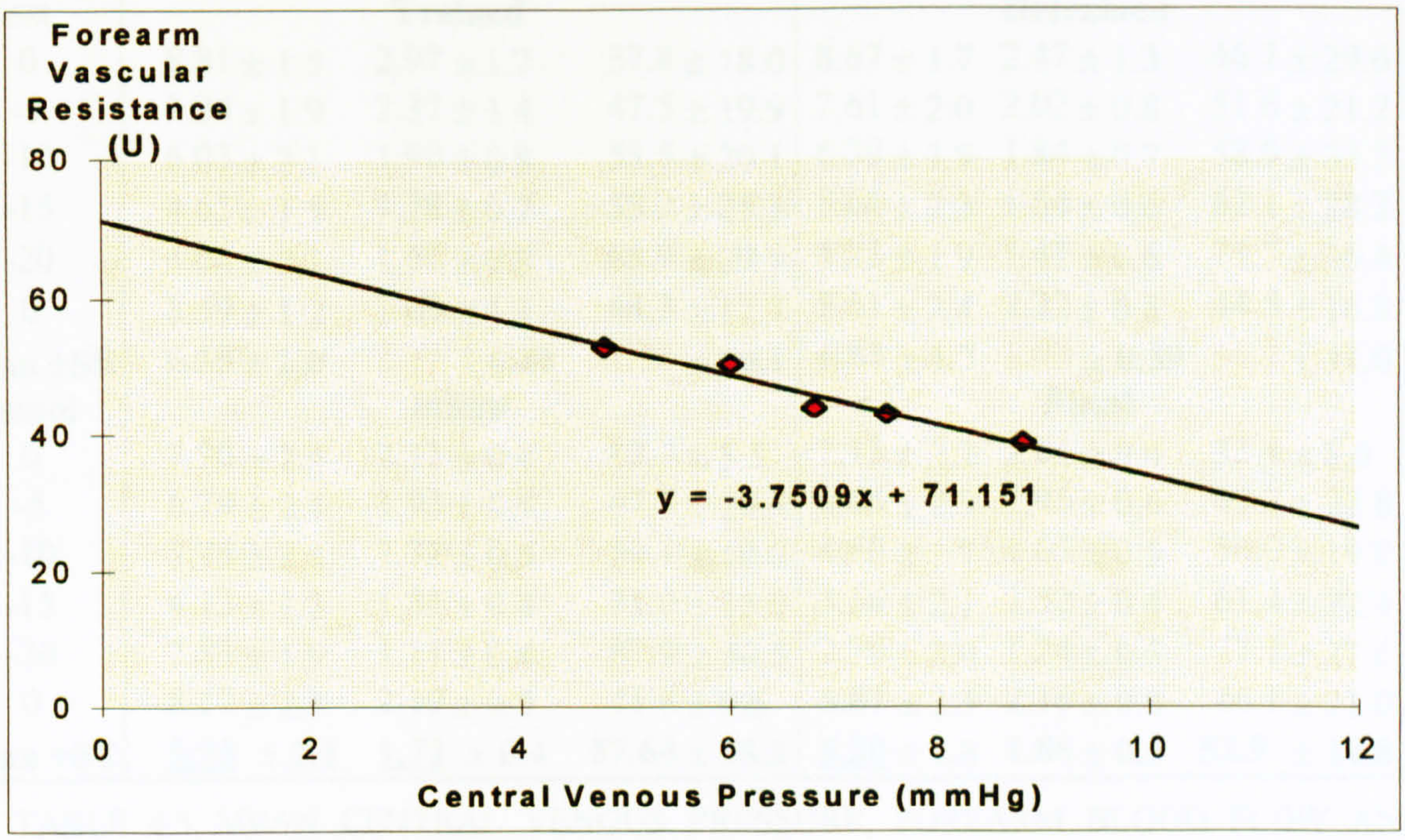


FIGURE 4.7 FOREARM VASCULAR RESISTANCE FOR SUBJECT SE DURING LOWER BODY NEGATIVE PRESSURE. The mean 8 measures of the ratio of mean arterial pressure and forearm vascular resistance (mmHg/ml.dl^{-1}min^{-1}) plotted against central venous pressure for 0, 5, 10, 15 and 20 mmHg LBNP.

Table 4.5 lists the mean central venous pressures, forearm blood flows and vascular resistances for each subject group measured during LBNP. The mean of the values recorded at each pressure (for each variable) was calculated to enable a general comparison between subject groups and trained state to be made.

- Test group forearm vascular resistance in the trained state was significant less (-8.9%) than that measured in the detrained state.
- Control group initial measurement of central venous pressure was significantly greater (+11.2%) than that observed in the final measurement.
- The mean test group trained and detrained venous pressures were significantly greater than those of both control measures (between 24% and 9.5%).
- Test group forearm blood flow in the trained state proved significantly greater than in the detrained state, both of which were significantly greater than the initial control value.

LBNP mmHg	Central Venous Pressure mmHg	Forearm Blood Flow $ml.dl^{-1}min^{-1}$	Forearm Vascular Resistance U	Central Venous Pressure mmHg	Forearm Blood Flow $ml.dl^{-1}min^{-1}$	Forearm Vascular Resistance U
Test		**Trained**			**Detrained**	
0	8.81 ± 1.5	2.97 ± 1.7	37.8 ± 18.0	8.67 ± 1.7	2.47 ± 1.3	46.7 ± 29.6
-5	7.24 ± 1.9	2.37 ± 1.4	47.5 ± 19.9	7.61 ± 2.0	2.02 ± 0.8	51.6 ± 21.2
-10	6.03 ± 2.1	1.90 ± 0.8	53.5 ± 20.1	6.39 ± 1.9	1.84 ± 0.7	58.9 ± 33.7
-15	4.61 ± 1.5	1.78 ± 0.7	58.2 ± 25.3	5.64 ± 2.3	1.64 ± 0.6	62.1 ± 28.2
-20	4.04 ± 2.2	1.60 ± 0.8	65.9 ± 29.9	4.23 ± 1.9	1.41 ± 0.6	73.7 ± 36.4
0	8.59 ± 1.2	2.09 ± 1.1	44.3 ± 17.7	8.51 ± 2.4	2.22 ± 0.8	44.5 ± 16.8
Mean ±SE	**6.55 ± 2.0**	**2.12 ± 0.49**	**51.26 ± 10.1**	**6.84 ± 1.7**	**1.93 ± 0.39**	**56.2 ± 11.0**
Control		**Initial**			**Final**	
0	7.90 ± 2.4	2.11 ± 0.4	43.3 ± 8.5	7.13 ± 2.2	2.64 ± 0.4	33.4 ± 8.0
-5	6.79 ± 2.4	1.93 ± 0.4	47.7 ± 10.4	6.04 ± 2.3	1.95 ± 0.6	49.3 ± 22.8
-10	5.76 ± 2.4	1.72 ± 0.3	54.1 ± 10.0	4.80 ± 1.7	1.65 ± 0.5	56.0 ± 19.9
-15	4.13 ± 2.2	1.31 ± 0.4	71.0 ± 15.0	3.56 ± 2.1	1.52 ± 0.4	61.4 ± 22.4
-20	2.83 ± 1.9	1.11 ± 0.4	87.9 ± 30.5	2.79 ± 2.0	1.24 ± 0.5	77.1 ± 27.6
0	8.17 ± 2.3	2.19 ± 0.5	41.8 ± 9.6	6.87 ± 2.5	2.16 ± 0.8	46.1 ± 21.0
Mean ±SE	**5.93 ± 2.1**	**1.73 ± 0.4**	**57.64 ± 18.3**	**5.20 ± 1.8**	**1.86 ± 0.5**	**53.9 ± 14.8**

TABLE 4.5 MEAN CENTRAL VENOUS PRESSURE, FOREARM BLOOD FLOW AND FOREARM VASCULAR RESISTANCE DURING LOWER BODY NEGATIVE PRESSURE.
Red denotes a significant difference ($p < 0.05$) between trained and detrained states.
Blue denotes a significant difference ($p < 0.05$) between control initial and final states.
Underscore denotes control value is significantly different ($p < 0.05$) to both test group measures.

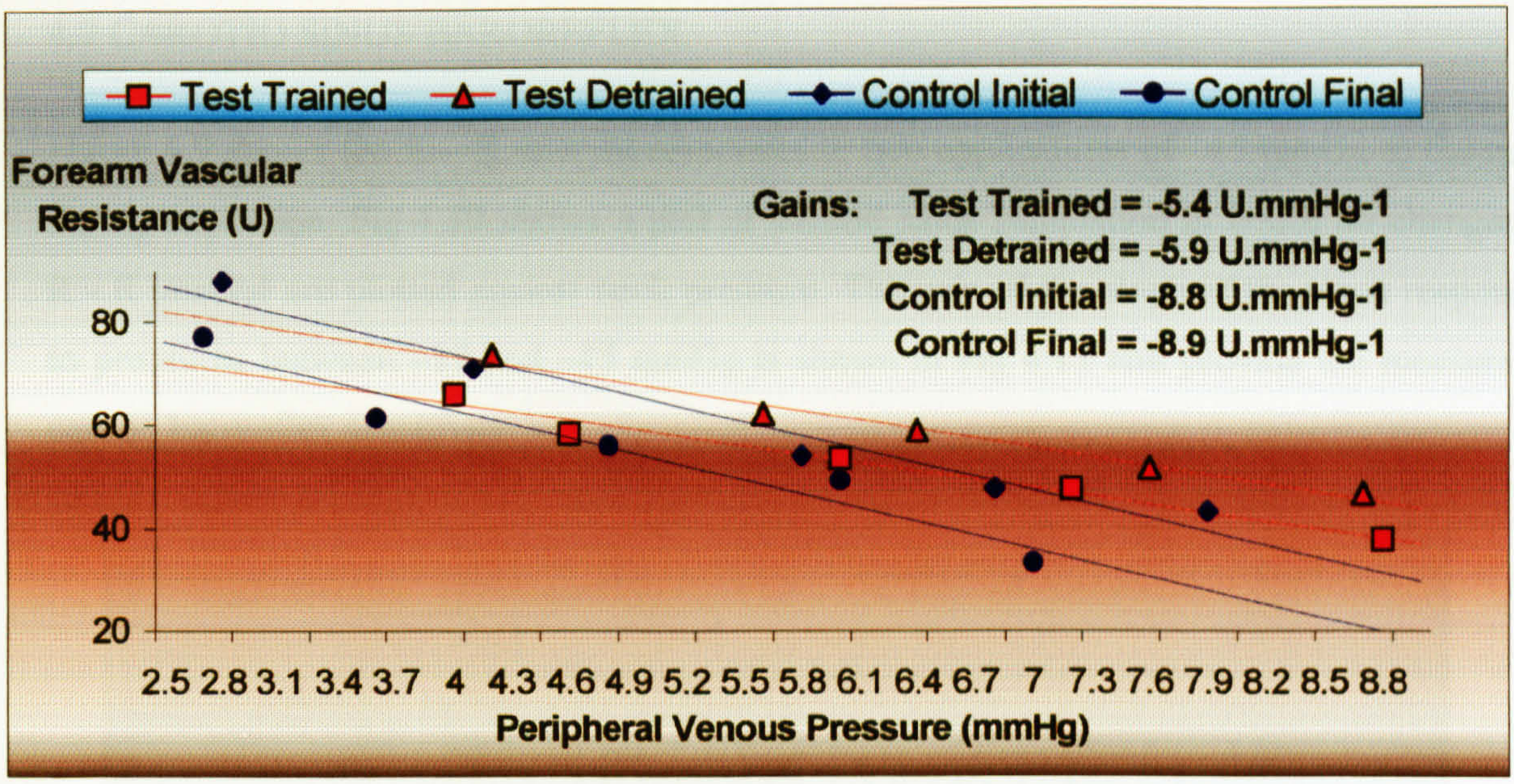


FIGURE 4.8 MEAN FOREARM VASCULAR RESISTANCE - VENOUS PRESSURE RELATIONSHIPS FOR CONTROL AND TEST GROUPS. Each data point represents the mean forearm vascular resistance/venous pressure value for the relevant subject group.

The mean slopes shown in Fig 4.8 indicate a trend towards lower sensitivity for the test group and differed slightly from the mean slopes calculated from the mean cardiopulmonary baroreflex sensitivity gains for the subject groups, as presented in Table 4.6. When comparing mean test group cardiopulmonary sensitivity in the trained and detrained states no significant changes in baroreceptor gain were noted. Similarly, no significant differences were noted between initial and final control group measures. Furthermore the test group mean gains for each state of training were not significantly different to those of the control group measures. Consideration of the test group measures as a whole irrespective of trained state i.e. mean $\dot{V}O_2max$ of 59 $ml.kg^{-1}min^{-1}$ (trained/detrained mean), showed that the test subjects has significantly lower gains than the control measures considered in unison.

	Control Group (n = 7)		Test Group (n = 7).	
	Initial	Final	Trained	Detrained
Gain, $U.mmHg^{-1}$	-8.37 ± 4.5	-7.78 ± 3.23	-6.09 ± 3.62	-4.90 ± 1.9
Grand Mean Gain	**-8.09** ± 3.77		**-5.49** ± 2.84	

TABLE 4.6 MEAN CARDIOPULMONARY BAROREFLEX GAIN FOR TEST AND CONTROL GROUPS (Mean ± SE).
Red signifies a significant difference ($p < 0.05$) between control and test group combined values.

4.7 CAROTID SINUS BAROREFLEX.

Figure 4.9 shows the R – R interval responses to two applications of –45 mmHg to the neck during expiration. Fig 4.10 shows a plot of carotid sinus stimulation in which all changes in R - R interval are plotted against neck pressure. The gain of the slope of the mean responses to pressures between –17 and –45 mmHg is shown in Fig 4.11 and provide the measure of carotid baroreflex sensitivity.

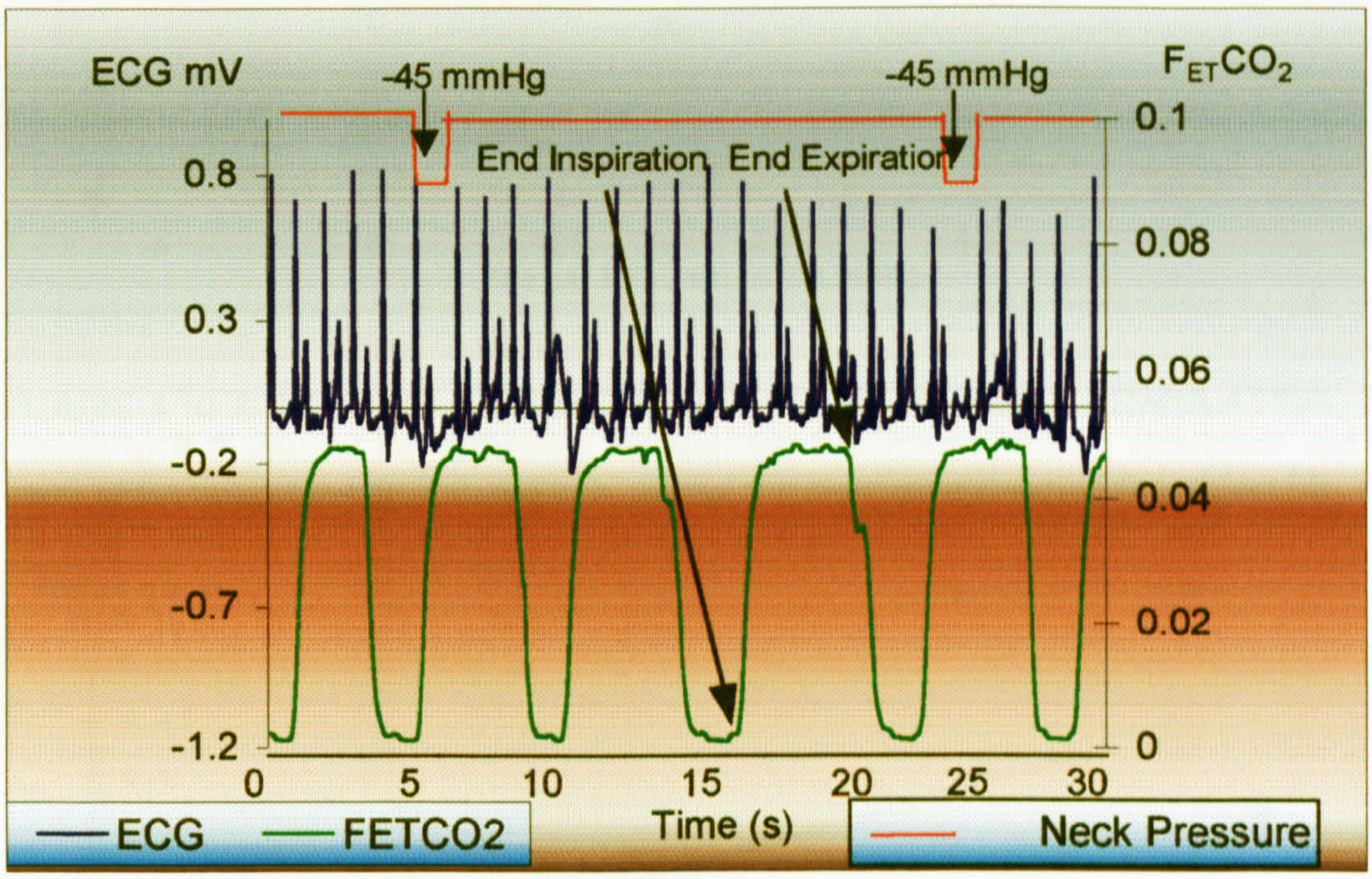


FIGURE 4.9 EXAMPLE OF R-R INTERVAL RESPONSE TO CAROTID SINUS STIMULATION. Two brief applications of –45 mmHg pressure to the neck are shown above a section of ECG trace. The stimuli were timed to correspond with expiration. R – R interval lengthening can be observed during each stimulus.

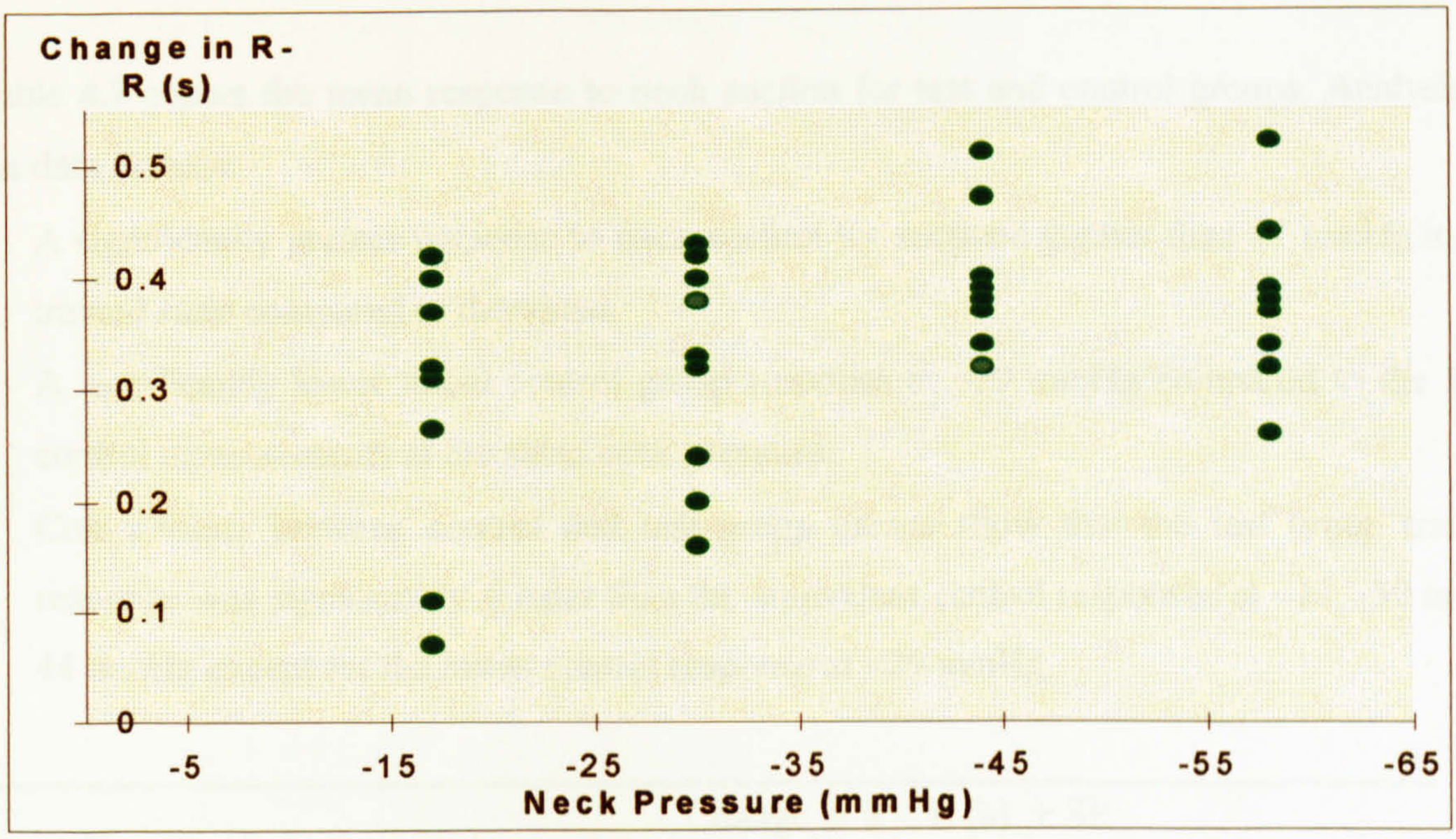


FIGURE 4.10 R-R INTERVAL RESPONSES TO CAROTID SINUS STIMULATION. The change in R-R interval i.e. difference between the R-R interval during simulation and the mean of the two preceding R-R intervals, during one experimental period for subject SE.

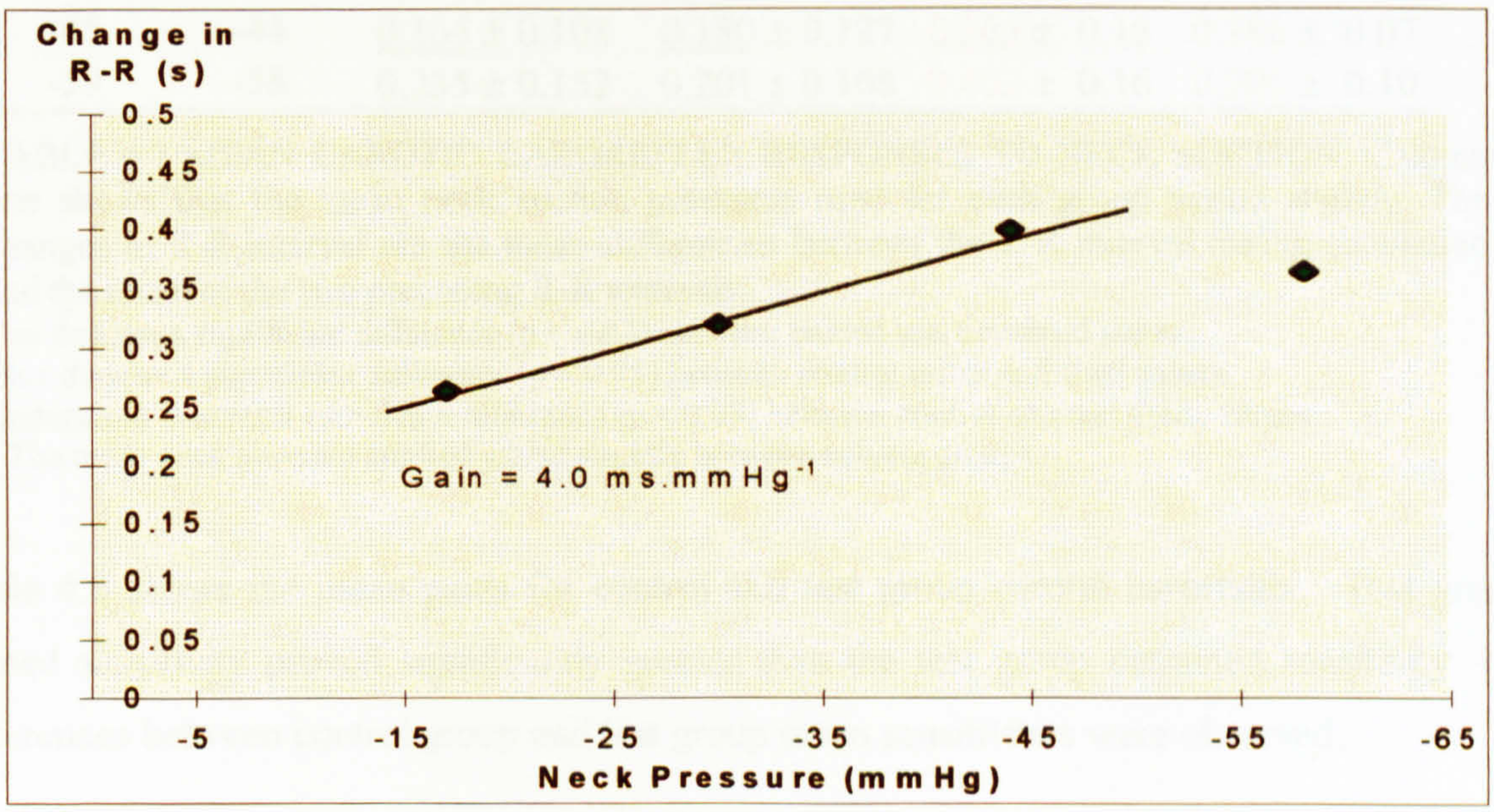


FIGURE 4.11 MEAN R-R INTERVAL RESPONSES TO CAROTID SINUS STIMULATION. The mean of the data presented in Fig 4.10 is shown in addition to the slope of the relationship between mean responses and neck suction less than 50 mmHg. The slope provides the measure of carotid baroreflex sensitivity.

Table 4.7 shows the mean response to neck suction for test and control groups. Analysis of the data reveals:

- A significantly greater response to neck suction for suctions greater than 17 mmHg in the trained state compared to detrained.
- A significantly lower initial control group response at –29 mmHg compared to the final control measurements at the same neck pressure.
- Comparisons between control and test group means show that the test group trained response was significantly greater than the equivalent control responses at –17, -30 and –44 mmHg except for the initial control response at –29 mmHg.

*Neck Pressure (mmHg)**		Change in R – R (s) ± SE			
		Control Group (n = 7)		Test Group (n = 7)	
		Initial	Final	Trained	Detrained
Control	Test				
-18	-17	0.095 ± 0.063	0.081 ± 0.07	0.208 ± 0.11	0.112 ± 0.05
-29	-30	0.156 ± 0.116	0.122 ± 0.131	0.290 ± 0.14	0.160 ± 0.07
-45	-44	0.165 ± 0.108	0.180 ± 0.127	0.365 ± 0.16	0.186 ± 0.07
-59	-58	0.235 ± 0.152	0.201 ± 0.108	0.402 ± 0.16	0.206 ± 0.10

TABLE 4.7 MEAN CAROTID BAROREFLEX RESPONSES TO NECK SUCTION. Column one shows that the mean neck suction pressures used for each group varied slightly. The changes in R-R interval are the mean differences between the R-R interval during simulation and the mean of the two preceding R-R intervals.
Red denotes a significant difference ($p < 0.05$) between trained and detrained states.
Blue denotes a significant difference ($p < 0.05$) between control initial and final values.
Underscore denotes a significant difference ($p < 0.05$) between control and test group values
* The mean neck pressure applied varied slightly between subject groups.

Table 4.8 shows the mean gains for control and test group carotid baroreflex. Test group trained sensitivity proved significantly greater than the test group detrained sensitivity. No differences between control group and test group mean sensitivities were observed.

	Control Group (n = 7).		Test Group (n = 7).	
	Initial	Final	Trained	Detrained
Gain, $ms.mmHg^{-1}$ Mean ± SE	2.54 ± 2.08	3.14 ± 2.39	5.44 ± 3.37	2.46 ± 1.02

TABLE 4.8. TEST AND CONTROL GROUP MEAN CAROTID BAROREFLEX SLOPES.
Red denotes a significant difference ($p < 0.05$) between test group trained and detrained states.

Fig 4.12 shows the mean carotid baroreflex slopes for each group. The more sensitive response for the test group when trained can be clearly seen as a steeper slope than those of the detrained state or control values.

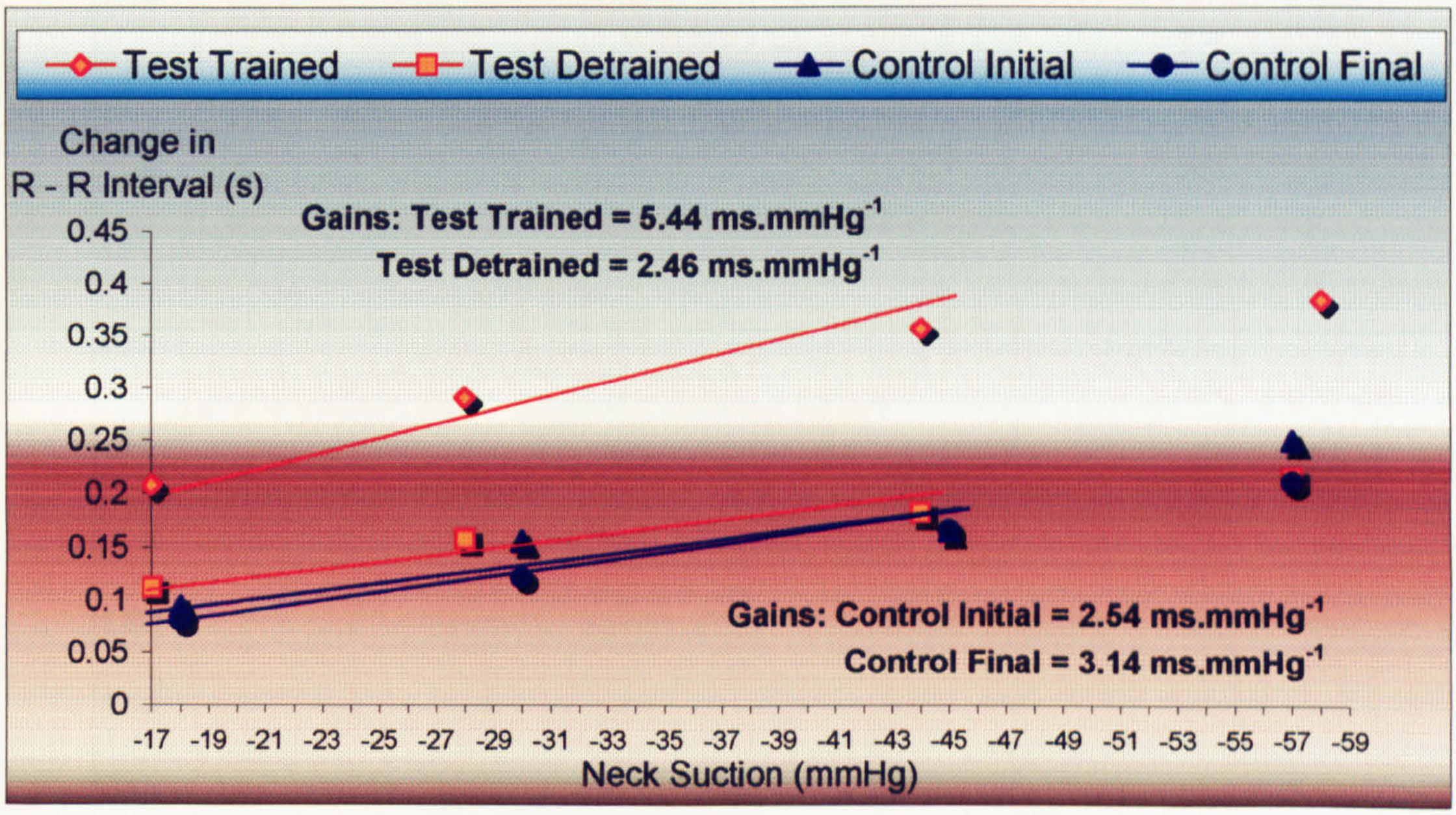


FIGURE 4.12 MEAN CAROTID SINUS BARORECEPTOR SLOPES FOR CONTROL AND TEST GROUPS.

4.8 INTEGRATED BAROREFLEX SENSITIVITY IN PARABOLIC FLIGHT

Seven subjects flew during the first parabolic campaign and eight during the second. One subject suffered from motion sickness during the latter half of the first campaign, after he had successfully performed his Valsalva's manoeuvres. Twenty five percent of the manoeuvres performed in-flight were not incorporated in the analysis because the relevant responses to the release of intrapulmonary pressure did not occur before the end of microgravity.

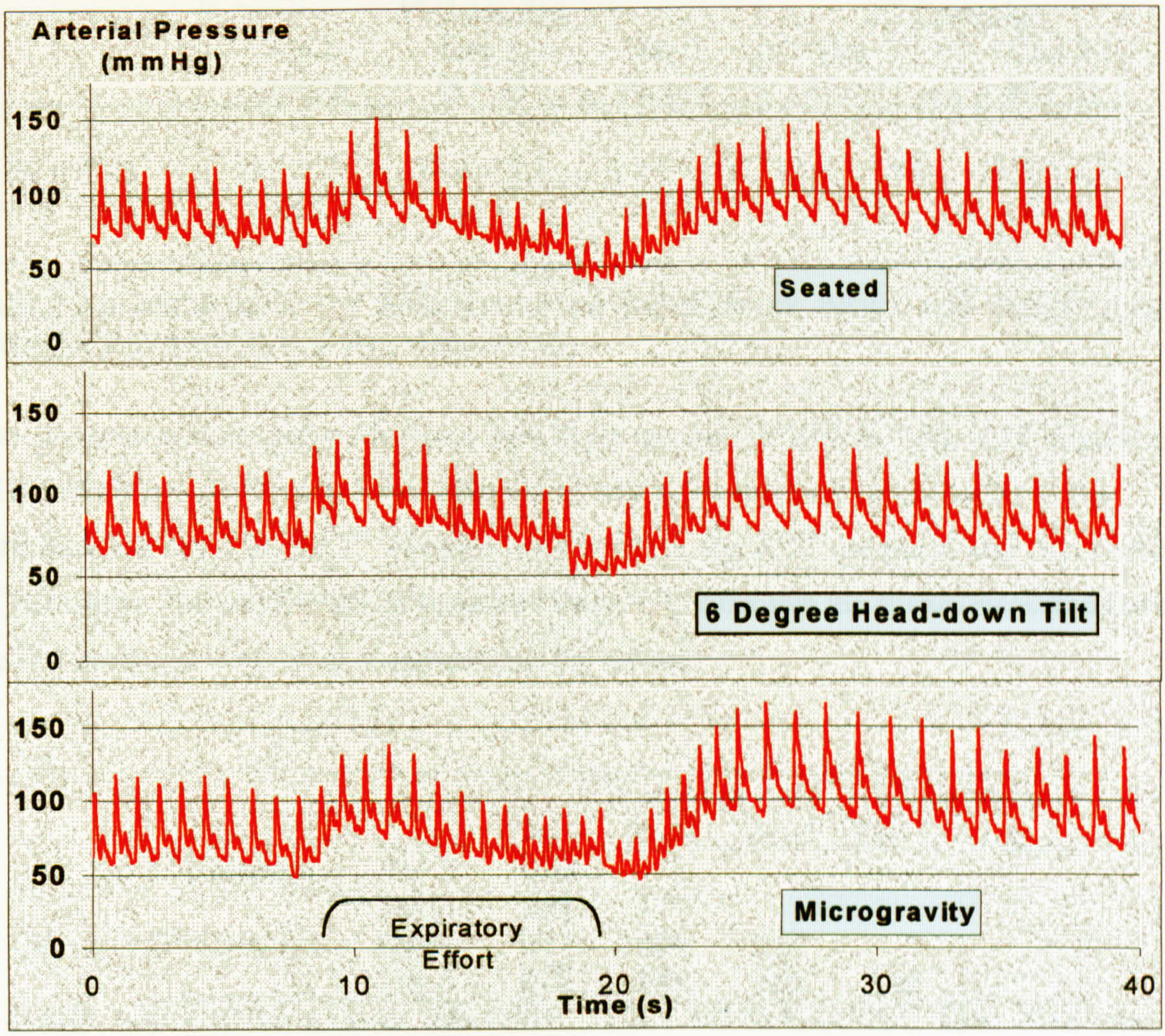


FIGURE 4.13 TYPICAL ARTERIAL PRESSURE RESPONSES TO VALSALVA'S MANOEUVRE ACCORDING TO POSTURE AND GRAVITY. Typical arterial pressure responses to a Valsalva's manoeuvre conducted when seated and at 6° head-down tilt at +1G and during microgravity, respectively are shown.

Integrated Baroreceptor Function. A preliminary investigation of the relationships between systolic pressure and the lengths of succeeding R-R intervals of phase IV of the Valsalva's manoeuvre for six subjects showed a significantly stronger linear correlation between systolic pressure and the first R-R interval ($r = 0.88 \pm 0.09$) than with the second R – R interval ($r = 0.66 \pm 0.18$) or third interval ($r = 0.27 \pm 0.34$).

A comparison of the BRSI for one subject recorded during three flights of the first campaign and two flights of the second showed no significant difference between microgravity BRSI means (Table 4.9).

	1st Campaign			2nd Campaign	
	Day 1 (n = 7)	Day 2 (n = 4)	Day 3 (n = 3)	Day 1 (n = 5)	Day 3 (n = 6)
BRSI, ms.mmHg^{-1}	11.3 ± 2.2	14.6 ± 2.2	14.3 ± 1.99	12.8 ± 1.68	11.8 ± 3.27
Coefficient of Variance	19.4	15.1	13.9	35.2	27.7

TABLE 4.9. MICROGRAVITY BARORECEPTOR SENSITIVITY INDEX FOR SUBJECT SE FOR FIVE PARABOLIC FLIGHTS (MEAN ± SE).

The strengths of relationships between each flight day can be seen in Table 4.10. Significant relationships ($p < 0.01$) were noted between all sets of manoeuvres except between day 1, 1st campaign and day 1 of the 2nd campaign and between day 2, 1st campaign and day 3 of the 1nst campaign. The coefficients of variance (Table 4.9) show that the BRSIs measured during the first campaign were more consistent than the second.

		1st Campaign			2nd Campaign	
		Day 1	Day 2	Day 3	Day 1	Day 3
1st Campaign	Day 2	**0.83**				
	Day 3	**0.99**	0.73			
2nd Campaign	Day 1	0.77	**0.99**	**0.88**		
	Day 3	**0.87**	**0.84**	**0.99**	**0.83**	

TABLE 4.10 CORRELATIONS BETWEEN MEAN MICROGRAVITY BRSI FOR ONE SUBJECT FOR FIVE PARABOLIC FLIGHTS.
Underscore denotes a significant relationship; 'r' ≥ 0.811 at 0.05 and 'r' ≥ 0.917 at 0.01

Pre Valsalva's Manoeuvre Baseline Measures. Table 4.11 shows the mean baseline heart rates and arterial pressures measured during 5 s immediately before the start of the Valsalva's manoeuvre performed when supine at 1G, +1.8G in-flight and when at head-down tilt, conducted by one subject for each flight day of the 1st campaign. Head-down tilt measurements were taken from the pre-flight head-down tilt data. Mean heart rate at +1Gx proved significantly greater than that of head-down tilt and +1.8Gx.

	Day 1 (n = 3)	Day 2 (n = 3)	Day 3 (n = 3)	Mean of Days 1-3
Heart Rate, bpm				
HDT	72.0 ± 9.0	69.0 ± 5.2	74.3 ± 4.0	71.8 ± 6.0
+1.8Gx	71.0 ± 6.2	67.7 ± 1.5	69.3 ± 3.0	69.2 ± 3.8
+1Gx	86.0 ± 4.6	80.0 ± 4.6	73.3 ± 4.2	79.8 ± 6.7
Mean Arterial Pressure, mmHg				
HDT	116.0 ± 5.4	118.7 ± 6.8	113.0 ± 2.0	115.9 ± 5.1
+1.8Gx	97.7 ± 7.5	118.7 ± 11.0	104.3 ± 7.5	106.9 ± 12.0
+1Gx	94.0 ± 6.9	116.0 ± 12.2	101.0 ± 11.5	103.7 ± 13.3

TABLE 4.11 BASELINE HEART RATES AND ARTERIAL PRESSURES FOR SUBJECT SE FOR THREE SUCCESSIVE PARABOLIC FLIGHTS (MEAN ± SE).
Underscorer = Significantly different ($p < 0.05$) to HDT and +1.8Gx mean heart rates
HDT = Head-down Tilt. All results are referred to heart level.

Group Pre Valsalva's Manoeuvre Baseline Condition Variables. When at +1G and +1.8G arterial pressures were corrected to heart level to account for the vertical height difference between finger and heart. The group mean arterial pressures and heart rates (measured for 5 s before Valsalva's manoeuvre) were not significantly different between the three conditions.

Responses to Valsalva's Manoeuvre. Table 4.12 lists the microgravity, head-down tilt and seated mean BRSIs for each of the parabolic campaigns. No significant differences were found between Campaign 1 pre-flight and post-flight measures for each +1G posture and thus Table 4.12 lists the combined pre/post-flight values. No significant differences during the Valsalva's manoeuvre phase I or phase III responses were found between conditions. Maximum phase IV systolic blood pressures were not significantly different between conditions, however, examination of the systolic pressure increases from the end of Valsalva's manoeuvre phase II to maximum systolic pressure in phase IV (distance between horizontal green lines Fig 4.14) showed a significantly greater increase in pressure during microgravity than that recorded during head-down tilt (+29.7 mmHg).

For the second campaign, with the exception of the post-flight pre-manoeuvre heart rates being less than ($p < 0.05$) the pre-flight pre-manoeuvre heart rates for the head-down tilt (-4.7 bpm) and seated (-2.4 bpm) positions, all pre and post Valsalva's manoeuvre measures

were also similar and thus the pre and post baseline measures were also averaged to give a combined mean (Table 4.12). As with the first campaign the change in systolic pressure between phase II and phase IV of the Valsalva's manoeuvre (+32.6 mmHg) proved significantly greater during microgravity than that observed during head-down tilt.

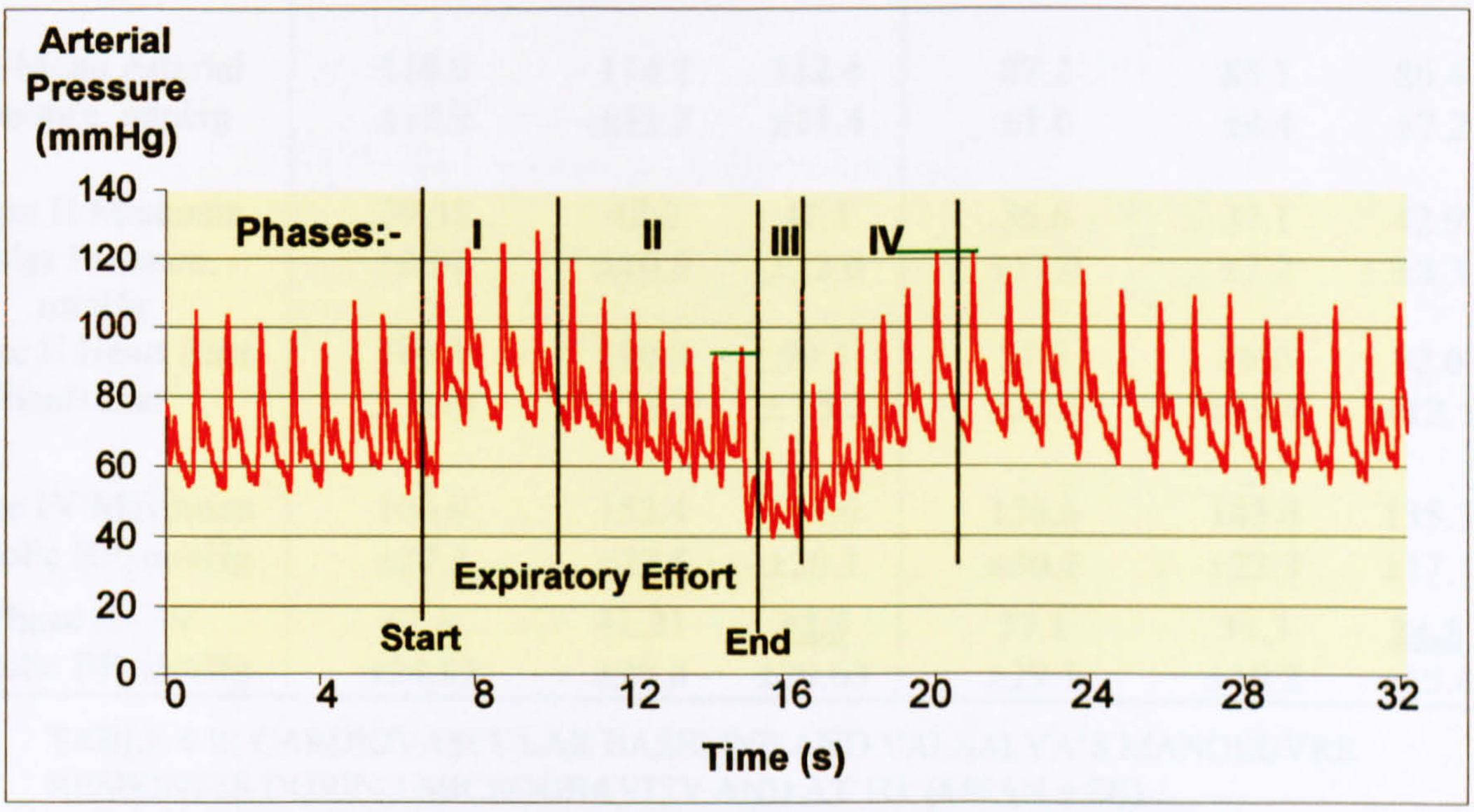


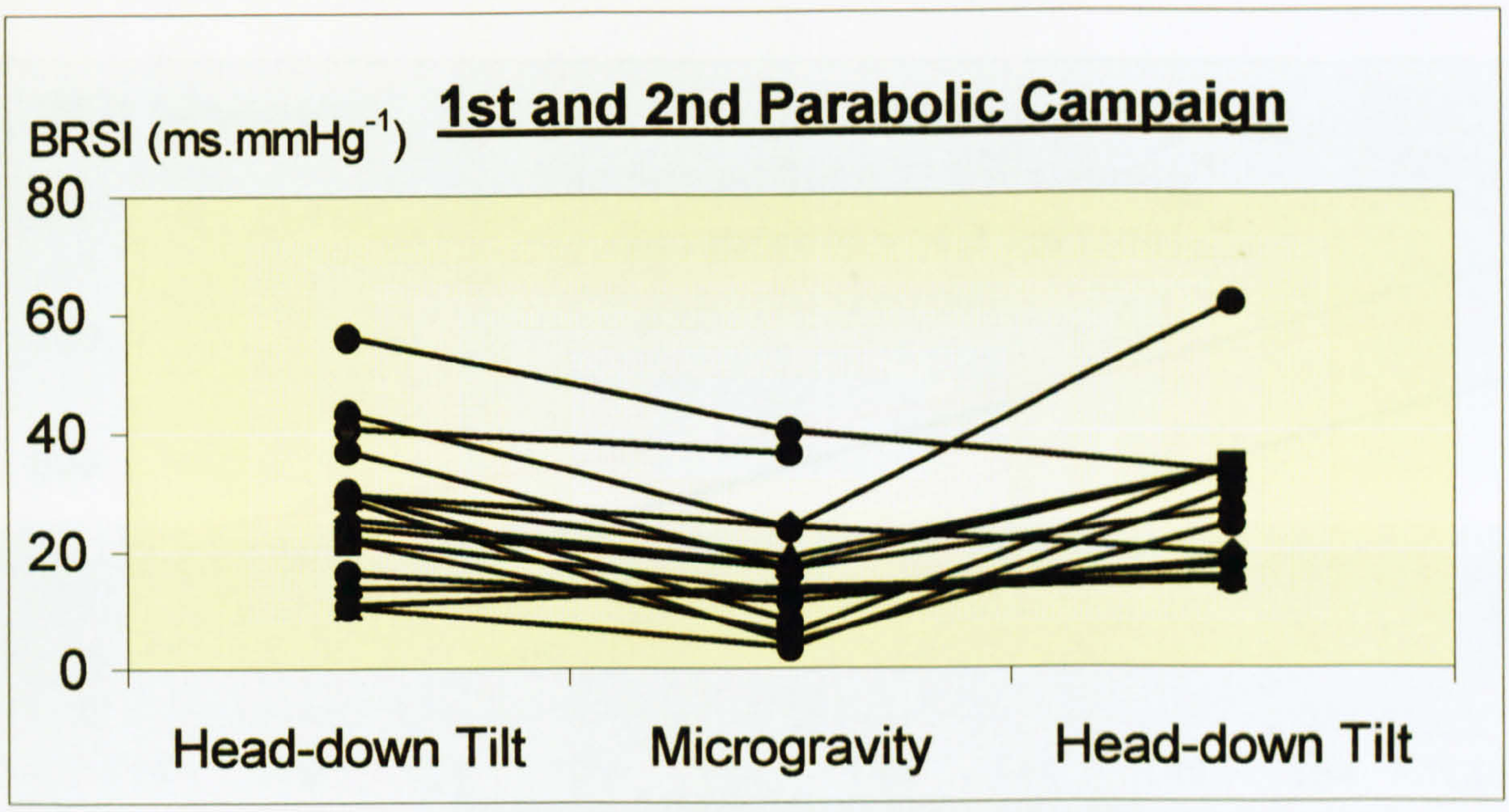
FIGURE 4.14 TYPICAL ARTERIAL PRESSURE RESPONSE TO VALSALVA'S MANOEUVRE. The only difference noted between microgravity and $+1G_z$ arterial pressure responses was a significantly greater change in systolic arterial pressure between phase II and phase IV of the response during microgravity.

	1st Campaign 'Combined pre+post'			2nd Campaign 'Combined pre+post'		
	Microgravity	Seated	HDT	Microgravity	Seated	HDT
Pre-Heart Rate Beats.min^{-1}	79.44 ±11.24	81.44 ±10.9	73.2 ±8.4	70.1 ±15.6	65.1 ±10.8	63.7 ±8.1
Pre-Mean Arterial Pressure, mmHg	116.9 ±13.9	114.7 ±11.2	112.4 ±11.4	87.2 ±1.6	85.1 ±4.4	86.4 ±7.2
Phase II Minimum Pulse Pressure, mmHg	39.35 ±6.07	42.0 ±10.9	47.1 ±12.0	36.6 ±11.0	37.1 ±7.2	42.9 ±8.3
Phase II Heart Rate Beats.min^{-1}	106.1 ± 16.8	100.0 ± 18.2	90.3 ± 15.3	97.3 ±22.3	89.0 ±19.4	82.0 ±12.5
Phase IV Maximum Systolic BP, mmHg	166.8 ±27.2	153.4 ±27.5	144.6 ±20.1	156.6 ±30.2	143.6 ±23.3	135.3 ±17.1
Phase II - IV Systolic BP, mmHg	62.6 ±24.63	41.21 ±28.8	32.3 ±20.63	57.1 ±29.1	34.3 ±19.2	24.5 ±15.8

TABLE 4.12 CARDIOVASCULAR BASELINE AND VALSALVA'S MANOEUVRE RESPONSES DURING MICROGRAVITY AND AT 1G (MEAN ± SE).
Underscore denotes significantly different ($p < 0.05$) to microgravity value (1st Campaign).
Double Underscore denotes significantly different ($p < 0.05$) to microgravity value (2nd Campaign). HDT = Head-down Tilt

4.8.1 BARORECEPTOR SENSITIVITY INDEX.

Figures 4.15 and 4.16 illustrate the mean integrated baroreflex sensitivities measured for each subject during parabolic campaigns 1 and 2, comparing the pre and post flight ground measures with those recorded in flight during microgravity.



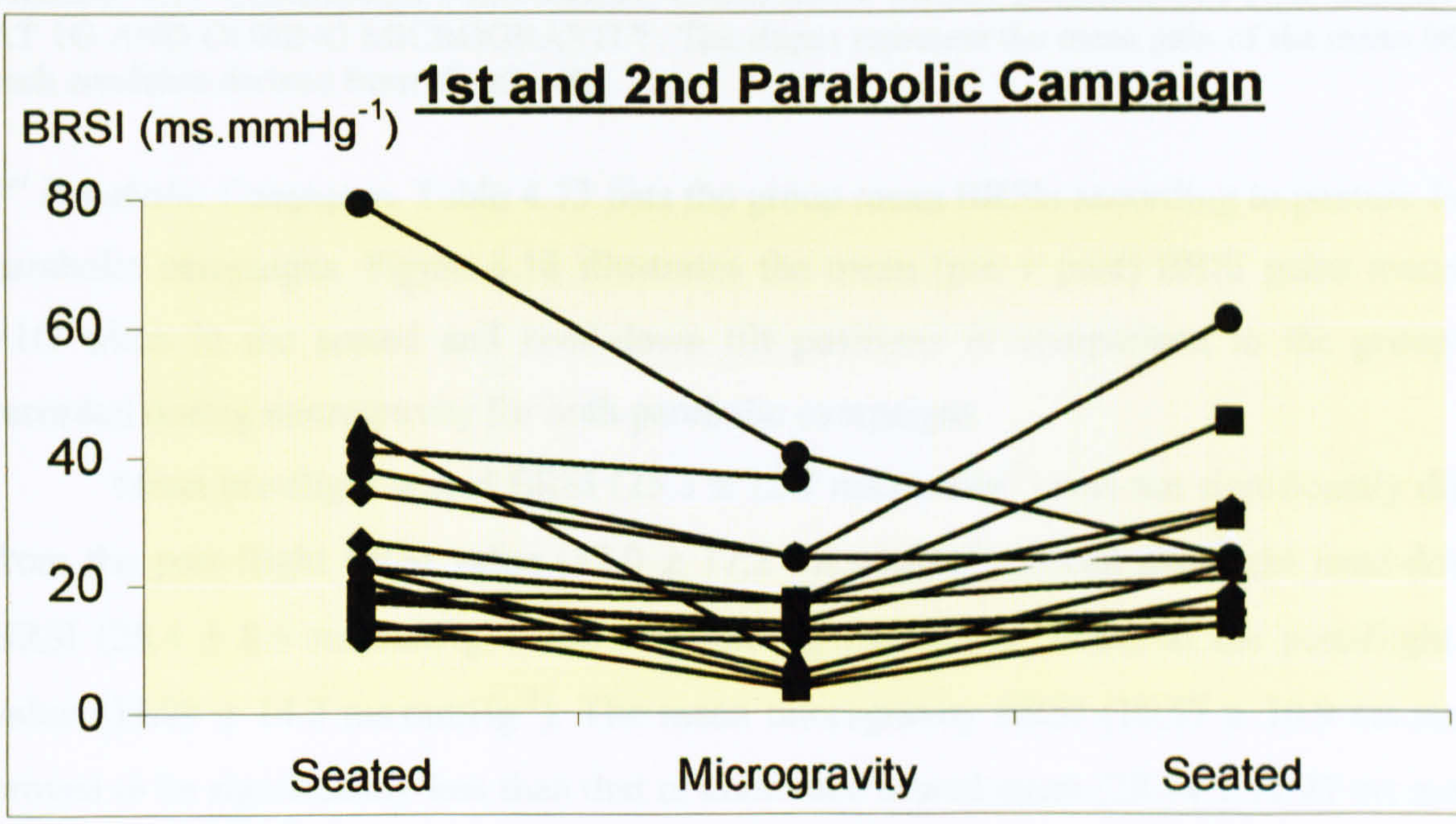


FIGURE 4.15 (ABOVE) AND 4.16 (BELOW) INDIVIDUAL BRSI MEANS. Each data point shows the mean BRSI for one subject according to posture and gravity condition.

Figure 4.17 shows mean BRSI slopes for the average microgravity, head-down tilt and seated position values for the combination of both parabolic campaigns.

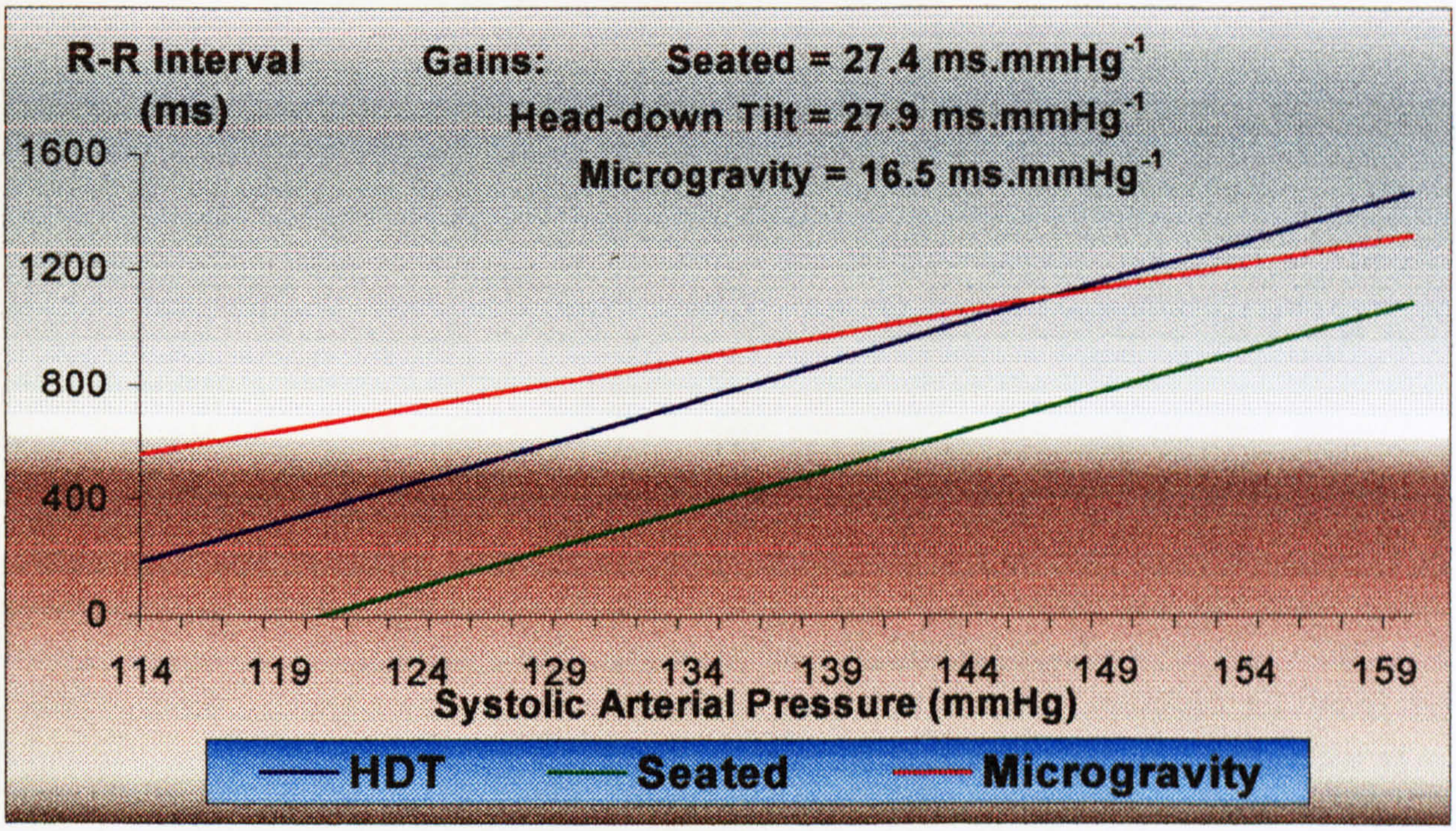


FIGURE 4.17 COMBINED PARABOLIC CAMPAIGN MEAN BARORECEPTOR SENSITIVITY AT 1G AND DURING MICROGRAVITY. The slopes represent the mean gain of the mean BRSI for each condition derived from all subjects.

1st Parabolic Campaign. Table 4.13 lists the group mean BRSIs according to posture for both parabolic campaigns. Figure 4.18 illustrates the mean (pre + post) BRSI gains recorded at +1G when in the seated and head-down tilt positions in comparison to the group mean recorded during microgravity for both parabolic campaigns.

Mean pre-flight seated BRSI (25.3 ± 12.7 ms.mmHg^{-1}) was not significantly different from the post-flight BRSI value (32.0 ± 17.2 ms.mmHg^{-1}). Mean pre-flight head-down tilt BRSI (28.4 ± 8.6 ms.mmHg^{-1}) was also not significantly different to the post-flight BRSI value (33.09 ± 14.2 ms.mmHg^{-1}). The mean microgravity BRSI (16.57 ± 10.9 ms.mmHg^{-1}) proved to be significantly less than that of combined seated mean (28.84 ± 12.27 ms.mmHg^{-1}) and combined head-down tilt (30.29 ± 9.29 ms.mmHg^{-1}).

2nd Parabolic Campaign. As with the first campaign mean pre-flight and post flight BRSI measures for the Seated (27.2 ± 20.6 ms.mmHg^{-1} and 24.6 ± 10.1 ms.mmHg^{-1} respectively) and head-down tilt positions (25.2 ± 14.5 ms.mmHg^{-1} and 25.7 ± 8.8 ms.mmHg^{-1}

respectively) were not significantly different to each other. The mean microgravity BRSI (16.3 ± 10.8 ms.mmHg^{-1}) proved to be significantly less than that of combined seated mean (25.9 ± 11.6 ms.mmHg^{-1}) and combined head-down tilt (25.5 ± 10.1 ms.mmHg^{-1}).

	Pre-flight			Post-flight		Combined Mean	
	HDT	Seated	Microgravity	HDT	Seated	HDT	Seated
Para Campaign 1, ms.mmHg^{-1}	28.4 ± 8.6	25.3 ± 12.7	16.6 ± 10.9	32.2 ± 12.3	32.4 ± 16.9	30.3 ± 9.3	28.8 ± 12.3
Para Campaign 2, ms.mmHg^{-1}	25.2 ± 14.5	27.2 ± 20.6	16.3 ± 10.8	25.7 ± 8.8	24.6 ± 10.1	25.5 ± 10.1	25.9 ± 11.6

TABLE 4.13 BRSI VALUES FOR +1G AND MICROGRAVITY CONDITIONS FOR BOTH PARABOLIC FLIGHT CAMPAIGNS (MEAN ± SE).
Para = Parabolic, HDT = Head-down tilt
Red indicates a significant difference ($p < 0.05$) to the microgravity mean.

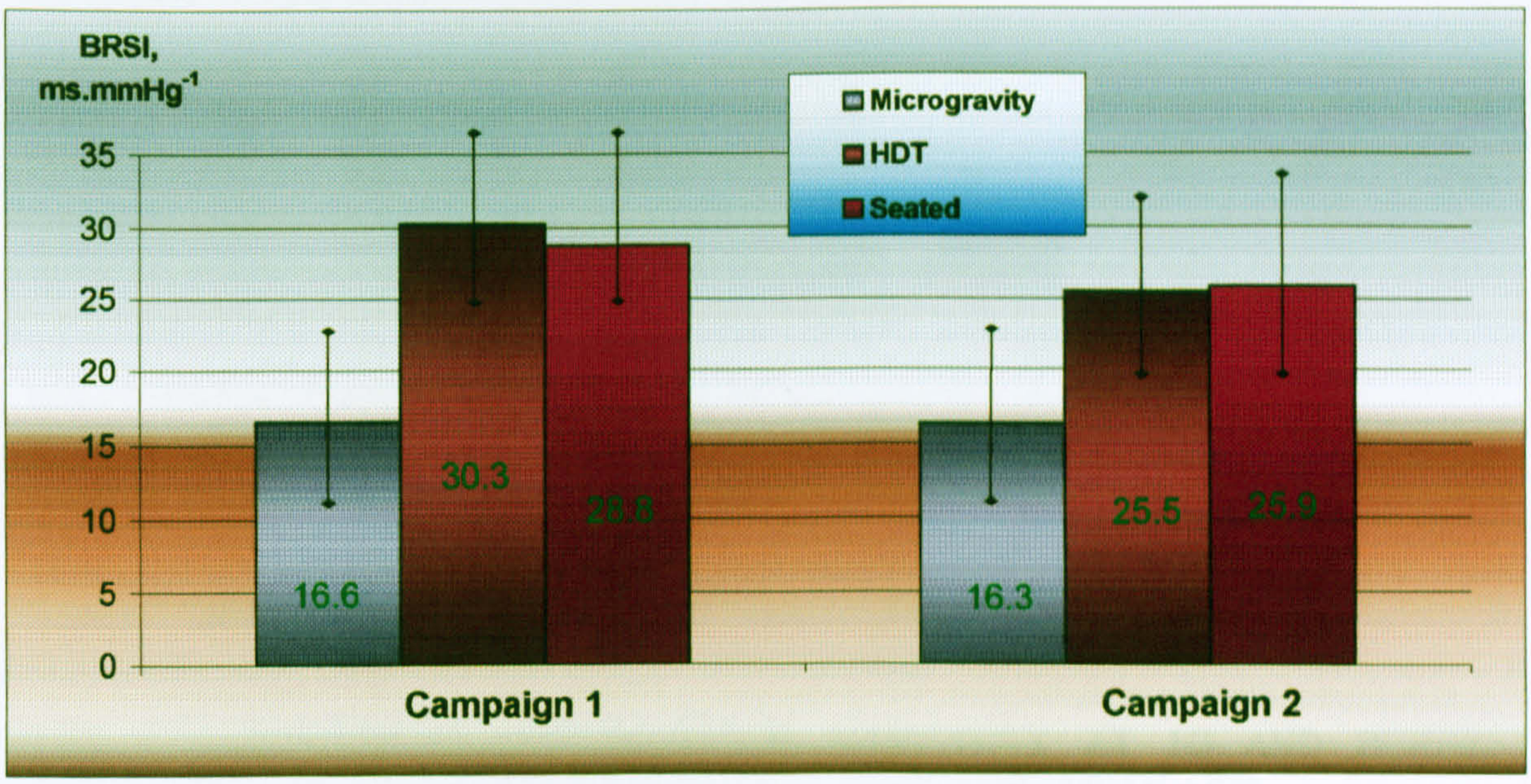


FIGURE 4.18 MEAN BARORECEPTOR SENSITIVITY INDEX AT 1G AND DURING MICROGRAVITY FOR FIRST AND SECOND PARABOLIC CAMPAIGNS.
HDT = Head-down Tilt

Effect of Trained State Upon Integrated BRSI. Table 4.14 and Figure 4.19 show mean integrated BRSI values obtained during head-down tilt, when seated and during microgravity. An examination of group mean BRSI from both parabolic flights showed no significant alterations in sensitivity with changes in trained state. Similar values for head-down tilt, seated and microgravity conditions were recorded for each campaign irrespective

of fitness level. Mean microgravity BRSI was significantly less than both 1G conditions for trained and detrained states.

	Test Group Means ± SE (n = 7)	
	Detrained	Trained
Head-down Tilt	23.1 ± 5.8	25.9 ± 10.3
Seated	22.9 ± 6.6	24.8 ± 13.1
Microgravity	14.1 ± 6.6	13.2 ± 7.2

TABLE 4.14 INTEGRATED BARORECEPTOR SENSITIVITY INDEX ACCORDING TO TRAINED STATE AT 1G AND DURING MICROGRAVITY.
Red denotes significant difference ($p < 0.05$) to microgravity mean.

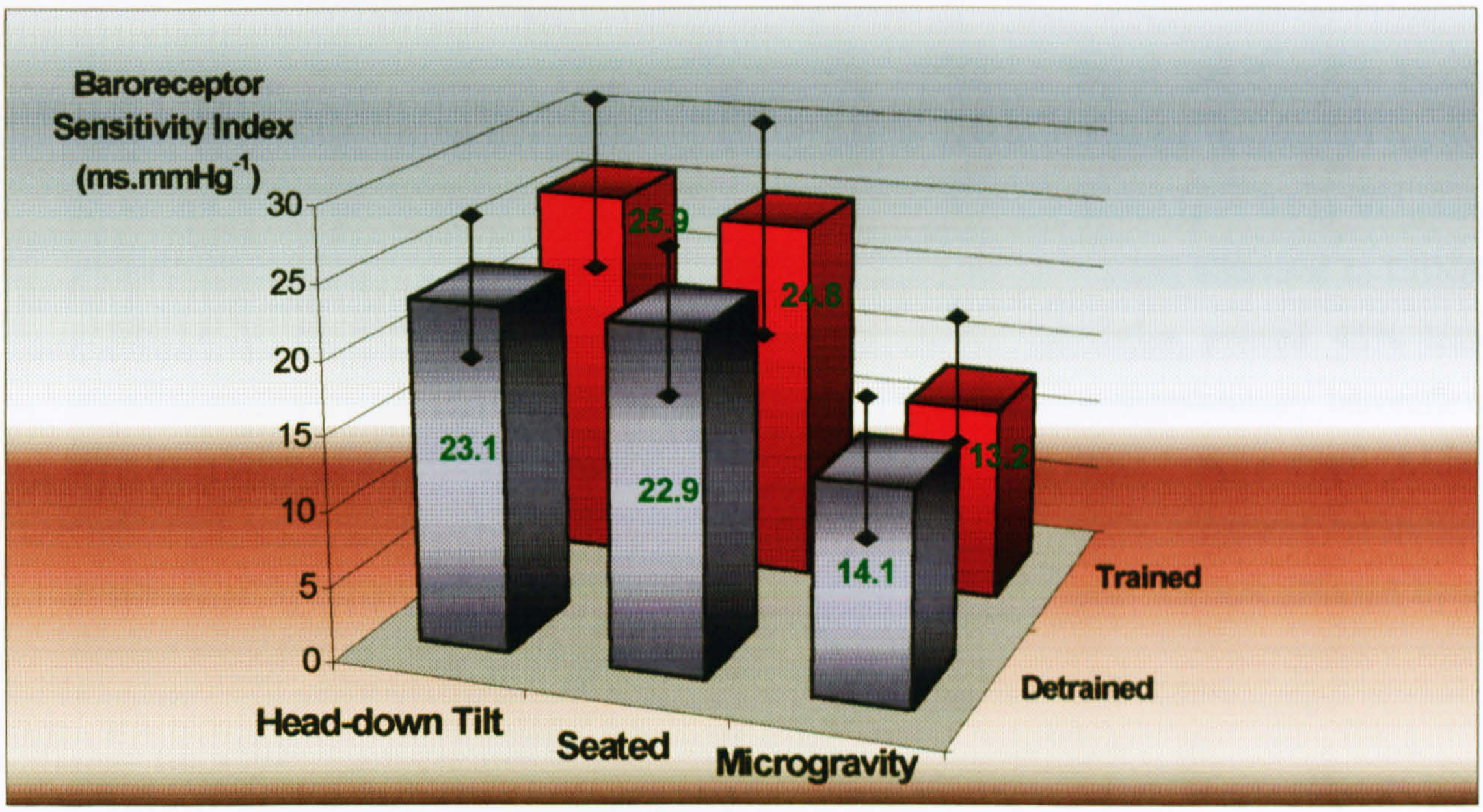


FIGURE 4.19 INTEGRATED BARORECEPTOR SENSITIVITY AT 1G AND DURING MICROGRAVITY FOR THE TRAINED AND DETRAINED STATES (MEAN ± SE).

Multiple Regression Analysis. A multiple regression analysis of all measured variables according to orthostatic tolerance (time to pre-syncope) for all subjects in all trained states revealed that forearm vascular resistance significantly ($p = 0.003$) predicted tolerance to LBNP, in addition to blood volume ($p = 0.01$), mean arterial pressure ($p = 0.041$), cardiopulmonary baroreflex gain ($p = 0.045$) and diastolic arterial pressure ($p = 0.047$). The model ($y = 0.0003x^2 - 0.1269x + 160.34$) derived indicated that the single reliable predictor was forearm vascular resistance.

5.0 DISCUSSION

Tolerance to an orthostatic challenge and carotid and cardiopulmonary baroreflex sensitivity were measured in seven subjects in exercise trained and detrained states to ascertain whether exercise training affects orthostatic tolerance and/or baroreflex function. Integrated baroreflex function was also measured when seated at 1G, during 1G simulation of the effects of microgravity (6° head-down tilt) and during actual microgravity, in the trained and detrained state, to investigate whether integrated baroreflex function during microgravity differs from that measured at +1G and to ascertain whether exercise training alters the integrated baroreflex response.

One objective of the study was to significantly alter endurance fitness and therefore blood volume in order to ascertain the effect upon tolerance to orthostatic stress. A mean 17 weeks of conditioning (detraining or retraining) resulted in significantly lower ($p < 0.01$) $\dot{V}O_2max$ (-15.6%) and blood volume (-8.1%) and significantly greater ($p < 0.05$) tolerance to LBNP (+22.9%) in the detrained state. Furthermore the carotid baroreflex proved 45% less sensitive ($p < 0.05$) in the detrained state and test group mean cardiopulmonary baroreflex gain (irrespective of fitness) was 32% less than ($p < 0.05$) the control group mean. Acute exposure to microgravity resulted in a 41% reduction ($p < 0.05$) of the integrated baroreflex response to Valsalva's manoeuvre whereas integrated baroreflex gain was not affected by a change in trained state during microgravity or at +1G.

5.1 ARTERIAL BAROREFLEX. The results of this study showed that the test subjects in a highly trained state had significantly greater carotid baroreflex gain than in the detrained state. Of eight previous studies designed to examine the effect of exercise training upon carotid baroreflex function using a neck suction technique, five indicate that sensitivity is increased in the trained state (Barney et al., 1988; Convertino et al., 1990a; Convertino and Fritsch, 1992; Eckberg and Fritsch, 1992; Tatro, 1992), two found no effect of trained state (Williamson and Raven, 1994; Raven et al., 1998) and one suggested a reduced gain with fitness (Stegemann et al., 1974). Stegemann and co-workers (1974) examined carotid sinus function by means of a neck and head pressure chamber employing changes in pressure in excess of 3 min to achieve a cardiovascular steady state. The primary difference reported

between their fit and unfit subjects was a less steep relationship between change in mean arterial pressure and neck pressure for the fit group. The difference between groups is far less evident when the gains of change in heart rate to change in neck pressure are considered. Although Stegemann and colleagues present their findings in bpm.mmHg^{-1} the maximum gains derived from neck pressures between –50 and –10 mmHg, when calculated using R-R interval for their fit subjects was approximately 2.0 ms.mmHg^{-1} and for their unfit subjects was 2.1 ms.mmHg^{-1}. The mean gain calculated from the results of the other seven studies is 3.8 ms.mmHg^{-1} (range 2.5 – 6.6 ms.mmHg^{-1}) irrespective of trained state. Baroreceptor function is such that the dynamic element of a response to stretch occurs quickly and transiently. The measure of response from a long stimulus after several minutes will consist solely of the adapted afferent discharge resulting from afferent activity from all receptor groups. Furthermore, the use of stimulus durations in excess of 3 min requires the subjects to breathe and thus the reduced efferent discharge associated with early inspiration would contribute to the baroreflex gain recorded. The afferent output elicited from a stimulus lasting 600 ms, however, will be greater due to the relatively large contribution from the dynamic response compared to all other elements of the total stimulus. With increasing magnitude of stimuli the cumulative response from brief pressure application will therefore be relatively greater thus producing a steeper slope. Consequently, the gains measured by Stegemann and colleagues (1974) are lower than that reported by other authors and may not, therefore, be comparable to those of carotid baroreflex studies employing a neck pressure method based on Eckberg principles.

The lack of any significant effect of change in trained state upon carotid baroreflex function as a result of 8 wk of deconditioning for the subjects of Raven and co-workers (1998) is not surprising. The authors report a reduction in $\dot{V}O_2max$ from 45 to 42 ml.kg^{-1}min^{-1} concomitant with a 4% decrease in blood volume. If a positive relationship exists between the two variables it is possible that the carotid sinus stimulation technique is not sensitive enough to detect a difference between the baroreflex measures extant for such similar states of fitness.

Williamson and Raven (1994) used subject groups with directly measured mean $\dot{V}O_2max$ values of 65 and 40 ml.kg^{-1}min^{-1}, and measured carotid baroreflex function by means of an Eckberg style lead collar. Although no significant difference in baroreflex gains was noted between subjects, the fit group had a mean of 6.4 ms.mmHg^{-1} whereas the unfit

group mean was 5.9 ms.mmHg^{-1}. The exact form of the relationship between carotid baroreflex gain and $\dot{V}O_2$max appears to be linear, however, if a curvi-linear or 'u' shaped relationship is the correct description, large changes in gain may occur between low and moderate fitness levels and between high and moderate levels, but when low and high levels of fitness are compared, little difference may be evident. Such a relationship could explain the results of Williamson and Raven (1994) (see Fig 5.3b page 143).

The indications are, however, that the greater carotid baroreflex sensitivities in the trained subjects (5.4 ms.mmHg^{-1}) compared to detrained (2.5 ms.mmHg^{-1}) in the present study are representative of that of the larger population of endurance athletes. Baroreflex gains of 4.0, 4.0, 3.7, 4.5 and 6.6 ms.mmHg^{-1} have been recorded in trained subject groups or the trained state (Barney et al., 1988; Convertino et al., 1990a; Convertino and Fritsch, 1992; Eckberg and Fritsch, 1992; Tatro, 1992). Gains in the less trained state or for less trained comparative groups were 2.5, 2.8, 2.5, 3.6, 5.4 ms.mmHg^{-1}, respectively. The greater degree of change found in the present study may be as a result of the higher level of aerobic fitness of the subjects when trained than those of the other studies relative to the detrained state.

The decrease in carotid baroreflex gain noted by Convertino and associates (1990) and Eckberg and Fritsch (1992) during periods of head-down tilt were attributed to reductions in parasympathetic baseline activity associated with the resulting deconditioned state. The reduced vagal component of the arterial baroreflex results in an attenuated response to blood pressure perturbations. Significant correlations were noted between the reduced carotid baroreflex gains and attenuated tachycardia and greater systolic pressure responses during orthostatic challenge (Convertino et al., 1990a). A significant correlation was also noted between baroreflex gain and tolerance to quiet standing, thus leading the authors' to suggest that reductions in vagally mediated carotid baroreflex responses as a result of deconditioning may contribute to reduced orthostatic tolerance (Convertino et al., 1990a; Eckberg and Fritsch, 1992).

Barney and colleagues (1988) reported that endurance trained subjects had significantly greater respiratory sinus arrhythmia indicative of augmented baseline vagal activity. The heightened sinus arrhythmia correlated significantly with $\dot{V}O_2max$ and thus was associated with the significantly greater carotid baroreflex gain found in the trained subjects. Although these authors did not measure orthostatic tolerance they postulated that a deficient baroreflex response did not contribute to orthostatic intolerance in trained individuals. Interestingly the augmented carotid baroreflex noted in the trained subjects of Tatro and co-workers (1992) was as a result of weight training rather than aerobic training, a form of exercise training not normally associated with an increase in baseline vagal activity. These authors also reported an increase in resting heart rate variability after training which paralleled the increased responsiveness of the vagally mediated carotid-cardiac reflex. This observation coupled with reduced systolic arterial pressures and calf venous compliance noted in most of the subjects (5 of 7) indicated the possibility of increased parasympathetic cardiac control despite a lack of change in resting heart rate. No alteration in tolerance to LBNP was recorded after training, however, and it was concluded that an augmentation of the carotid baroreflex was not advantageous during hypotensive challenge.

The findings of significant reductions in carotid baroreflex gain by Convertino and Fritsch (1992) after 14 d of detraining after the culmination of a 10 wk programme of aerobic training supports the contention that the arterial baroreflex response may be related to altered basal parasympathetic activity. Although the change in degree of fitness of the subjects was not reported, the pre-study $\dot{V}O_2max$ mean value of 41 $ml.kg^{-1}min^{-1}$ indicates that the subjects were of low to moderate fitness. The reduction of mean gain from 4.0 to 2.8 $ms.mmHg^{-1}$ for these subjects is in agreement with the magnitude of change in baroreflex gain noted in the present study of 5.4 to 2.5 $ms.mmHg^{-1}$.

5.2 CARDIOPULMONARY BAROREFLEX. The mean cardiopulmonary baroreflex gain measured in the trained state by studies employing the same technique as the present study was $-5.4\ U.mmHg^{-1}$ (Mack et al., 1987; Convertino et al., 1990b; Mack et al., 1991; Raven et al., 1998). The same investigations produced a mean reflex gain of $-3.4\ U.mmHg^{-1}$ for the detrained state. The values recorded in the present study for the trained and detrained states were -6.1 and -4.9 $U.mmHg^{-1}$ respectively. The mean control group slopes also appear high (-8.4 initially and $-7.8\ U.mmHg^{-1}$) in comparison to the control group mean of –6.2

$U.mmHg^{-1}$ recorded by Mack and colleagues (1987, 1991)[13]. The possibility exists, therefore that the methodology used in this study was either more sensitive than that of earlier work and was therefore able to measure the baroreflex response more accurately, or differs from that of other investigations such that a consistently greater measure was obtained. The techniques used for each of the earlier studies and the current investigation appear identical with the exception of the thermal environment used. All baroreflex measures were conducted using controlled conditions by means of a climatic chamber. The Yale University team maintained chamber temperature at 28° C, Raven and co-workers (1998) report using 24° C and although Convertino does not mention what temperature was used he was working with the Yale University team at the time and so is likely to have used 28° C. In the present study temperature was maintained at 21° C, therefore the higher gains may derive from a greater state of vascular constriction resulting from the cooler experimental condition. Thermoregulatory derived vasoconstriction should produce a systematic increase in vascular resistance irrespective of LBNP.

Fig 5.1 shows a plot of the relationship between baroreflex gain and $\dot{V}O_2max$ for each of the subject groups of the earlier studies considered in comparison to the current results. The relationships are very similar in both cases. The results of this study, however, are shifted up the ordinal axis in a manner suggestive of a systematic augmentation of vascular resistance as a result of the cooler conditions; consequently a difference in methodology may account for the slightly high cardiopulmonary baroreflex gains measured in the present study.

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[13] Yale University team

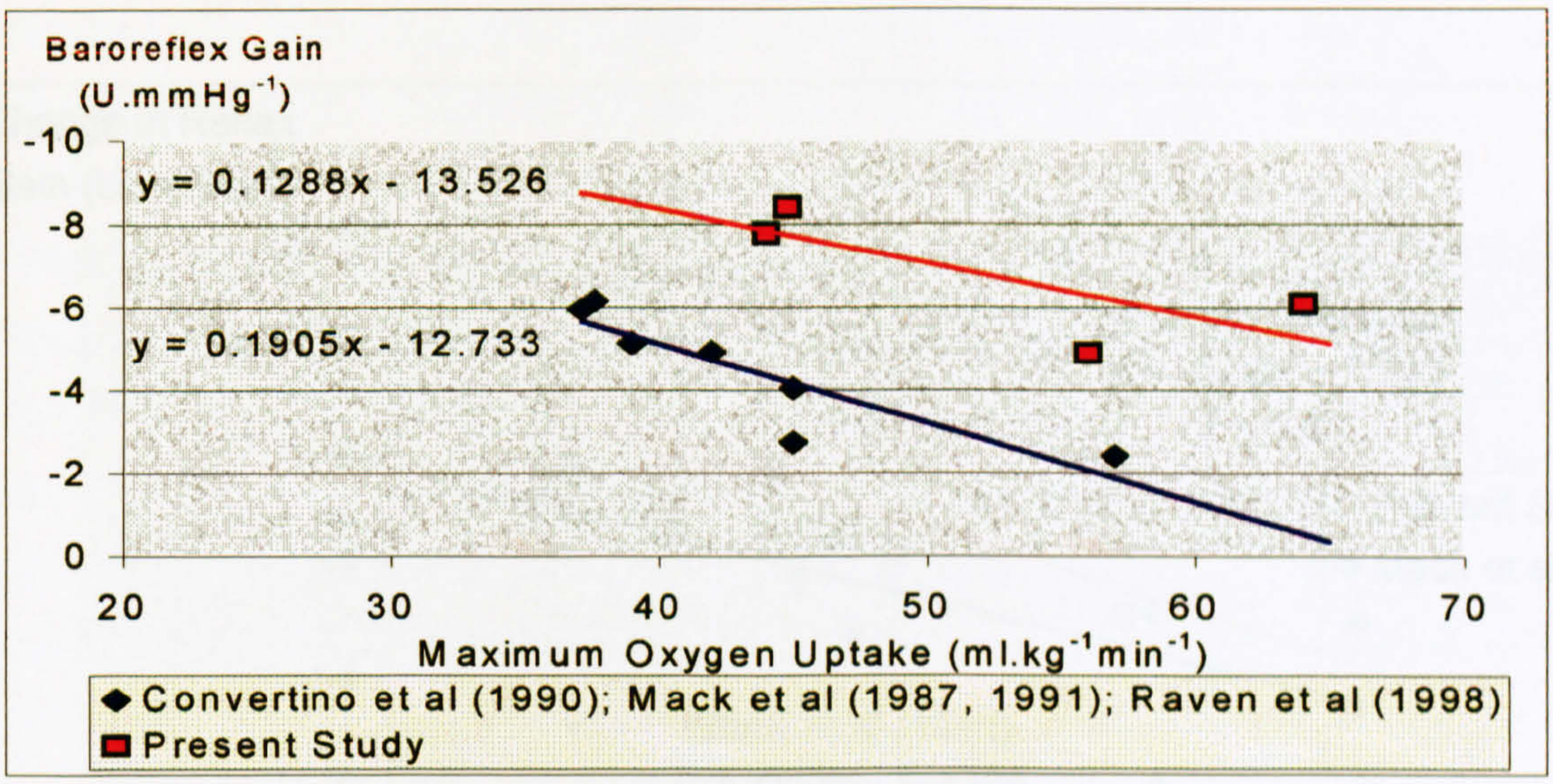

FIGURE 5.1. CARDIOPULMONARY BAROREFLEX GAIN/MAXIMUM OXYGEN UPTAKE RELATIONSHIPS FOR EACH SUBJECT GROUP OF 4 STUDIES CONSIDERED IN COMPARISON TO THE CURRENT INVESTIGATION. The relationships between $\dot{V}O_2max$ and cardiopulmonary baroreflex gain are very similar in both cases. The results of this study, however, are shifted up the ordinal axis in a manner indicative of a systematic augmentation of vascular resistance

Mack, Convertino and Nadel (1993) in their review of exercise training effects on the cardiopulmonary baroreflex, comment on the observation that a significant inverse relationship existed between training induced change in baroreflex gain and change in body weight relative blood volume[14]. Fig 5.2 shows a similar relationship between the results of this study and that of Mack and colleagues (1991) although the sample size in the present study is sufficiently affected by two outlying values to disallow significance ($r = 0.6$, $df = 6$, $p > 0.05$) whereas two outliers of Mack and colleagues (1991) do not effect their larger sample size to such an extent ($r = 0.65$, $df = 13$, $p < 0.05$). The delta cardiopulmonary baroreflex gain/delta blood volume relationship observed in this study, therefore, is in general agreement with that of previous literature.

[14] Blood volume (ml)/weight (kg)

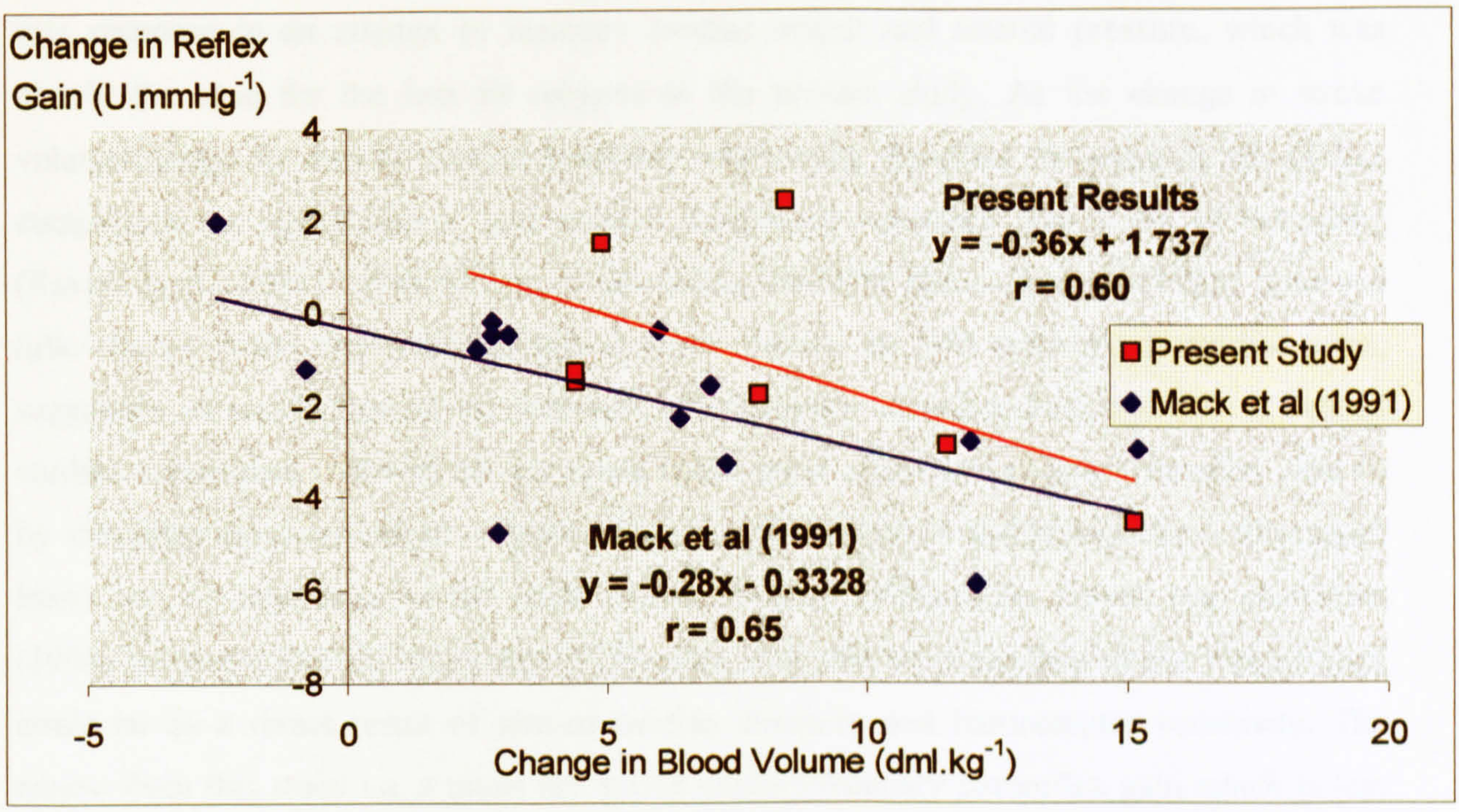

FIG 5.2 DETRAINING INDUCED CHANGE IN CARDIOPULMONARY BAROREFLEX GAIN TO CHANGE IN BLOOD VOLUME RELATIONSHIP. Test subject detraining induced changes in weight related blood volume according to change in cardiopulmonary baroreflex gain for the present study and that of Mack et al (1991). Both sets of data suggest the possibility of a relationship between cardiopulmonary baroreflex function and blood volume.

Central venous pressure at rest did not significantly change with detraining in the present study and the control group had significantly lower values than both trained states of the test group. Mean cardiopulmonary baroreflex gain also did not change significantly with detraining, but proved significantly less for the combined test group results than for the control group, thus suggesting an inverse relationship between central venous pressure and cardiopulmonary baroreflex gain. These results are in support of Mack and colleagues (1993) who report an association between decreased cardiopulmonary baroreflex gain and elevated resting central venous pressure and stroke volume with endurance training. The authors suggested that endurance training induced hypervolaemia and elevated cardiac filling pressures contribute to left ventricular hypertrophy and may lead to remodeling of cardiac tissue. Raven and associates (1998) found that detraining lead to a greater reduction in stroke volume per unit reduction in central venous pressure during LBNP i.e. that central venous pressure was maintained better than stroke volume during orthostatic stress in the

detrained state. A more profound reduction in stroke volume necessitates an augmented heart rate response in an attempt to maintain cardiac output and arterial pressure, which was clearly the case for the less fit subjects in the present study. As the change in stroke volume/change in central venous pressure relationship provides an estimate of cardiac compliance the implication is that cardiac compliance increases with 8 wk of detraining (Raven et al., 1998). After 15 wk of detraining, Hickson and colleagues (1985) observed little change in left ventricular internal diameter despite an 11% reduction in cardiac mass, suggestive of a reduction of the thickness of the cardiac chamber walls and thus increased cardiac compliance. Altered cardiac compliance could affect baroreceptor function directly by changing the visco-elastic coupling between the receptors and myocardium (discussed later) and by alterations in the heart pressure/volume relationship. Raven and associates (1998) proposed that the attenuated tachycardic response to orthostasis in the trained state could be as a direct result of altered cardiac structure and baroreceptor sensitivity. The results from this study i.e. a mean test group cardiopulmonary baroreflex gain which is less than that of untrained controls, agrees with the findings of earlier work and could be attributed to altered cardiac compliance.

5.3 BAROREFLEX GAIN – MAXIMUM OXYGEN UPTAKE RELATIONSHIP. When considering the results from the current study in addition to the mean reflex gains measured in 12 other studies[15] a binomial regression plot indicates the possibility of a curvi-linear relationship ($p = 0.045$) between $\dot{V}O_2max$ and carotid baroreflex sensitivity and negative linear relationships between $\dot{V}O_2max$ and cardiopulmonary and aortic baroreflex gains (Fig 5.3a). Similar carotid baroreflex gains for low fit (40 $ml.kg^{-1}min^{-1}$) and high fit (65 $ml.kg^{-1}min^{-1}$) subjects were observed by Williamson and Raven (1994) leading them to conclude that endurance fitness may not alter reflex gain. It may be that a confounding variable is affecting the results of the low fit/sedentary subjects. For example very low fitness levels could be associated with high arterial baroreflex gain as a result of hypertension[16]. A sufficient number of borderline hypertensive subjects if employed in the studies used in Fig 5.3a could cause the gain at the lower end of the abscissa to be elevated.

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[15] Mack et al (1987); Barney et al (1988); Convertino et al (1990); Levine et al (1991); Mack et al (1991); Convertino and Fritsch (1992); Shi et al (1993); Crandall et al (1994); Hughson et al (1994); Williamson et al (1994); Savard et al (1995); Raven et al (1998).

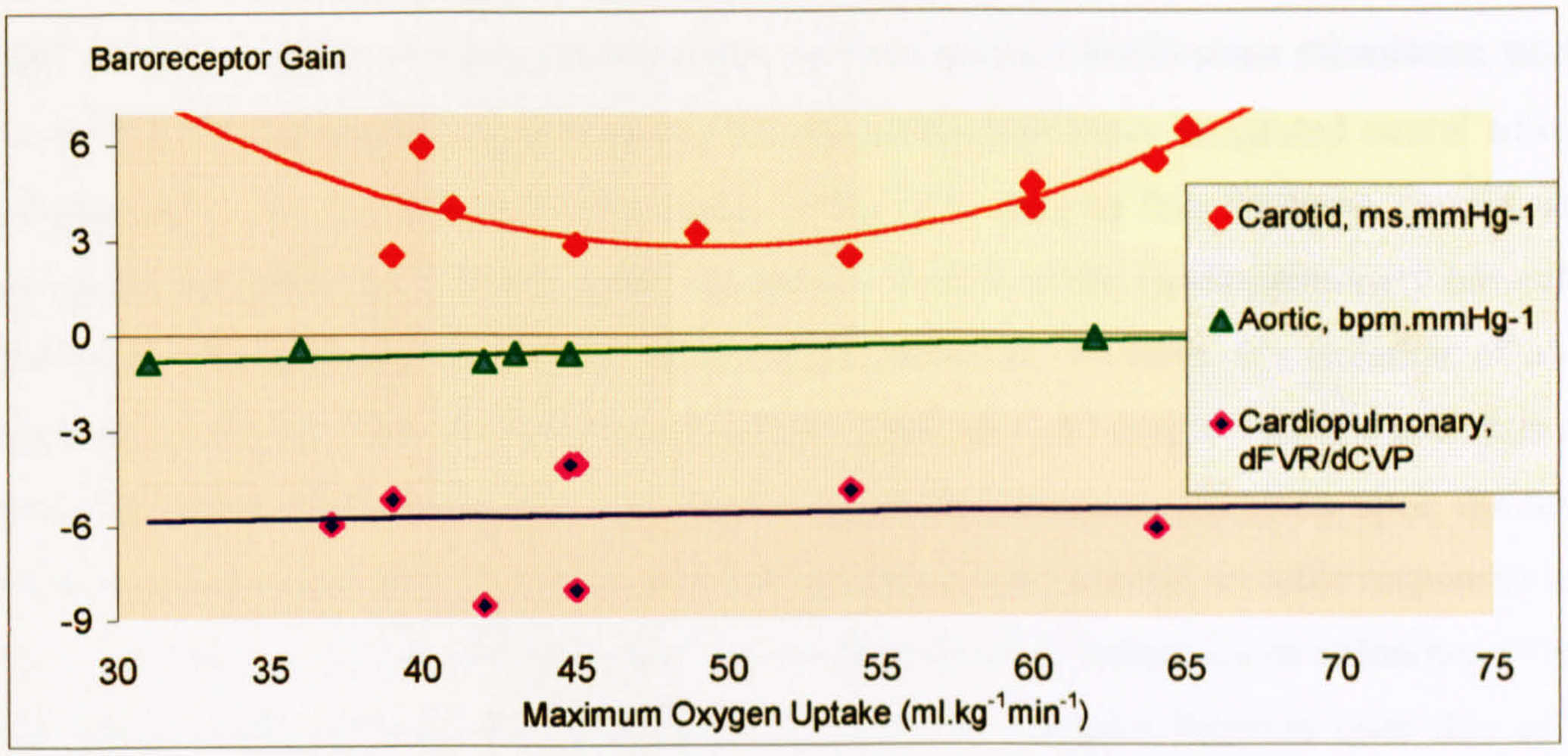

FIGURE 5.3a BARORECEPTOR GROUP GAIN / MAXIMUM OXYGEN UPTAKE RELATIONSHIP. The relationships between individual baroreceptor group function and $\dot{V}O_2max$ are plotted using the results of twelve[15] studies plus those of the present investigation. A binomial line of best fit proved to be a significantly stronger ($p = 0.045$) estimation of relationship between carotid sinus baroreflex sensitivity and $\dot{V}O_2max$ than a linear plot. Linear relationships with negative slopes were noted for cardiopulmonary and aortic baroreceptor sensitivity and $\dot{V}O_2max$.

Should these relationships be correct, consideration of the function of the reflex groups singularly implies that the moderately fit state offers reduced heart rate and vasoconstrictor responses by means of the carotid baroreceptor and that the aortic receptor group appears to provide a slightly greater gain for the low fit state than the high fit state, which due to its dominance over carotid function, may offer an elevated heart rate response overall in the less fit subjects during orthostasis in agreement with the findings of this study. The cardiopulmonary/$\dot{V}O_2max$ relationship suggests a stronger cardiopulmonary baroreceptor derived vasoconstrictor response in the low fit state than any state of greater fitness.

For a more accurate description of the reflexes the integrated responses per se should be considered. The findings of the earlier integrated baroreflex studies using animals and the human investigations of Victor and Mack (1986) and Potts and co-workers (1995) when considered in the light of the relationships shown above indicate that the inhibition of arterial baroreflex function by the cardiopulmonary baroreflex will be the least in the highly trained state. When assessing carotid baroreceptor function the usual procedure for carotid sinus stimulation does not involve the isolation of the stimulus-response from the possible tonic

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[16] The heightened level of sympathetic activity associated with hypertension may be sufficient to augment baroreflex gain (Tanji, 1992).

effect of the cardiopulmonary receptor group. That is, if the arterial reflex is attenuated by tonic cardiopulmonary activity the measures derived during carotid sinus stimulation studies are in fact the combined response of carotid and cardiopulmonary integrated neural activity. Consequently, the carotid sensitivity curve in Fig 5.3a may in fact illustrate carotid sinus sensitivity according to $\dot{V}O_2max$ under the tonic influence of the cardiopulmonary baroreflex inhibition. The measurement of the aortic reflex, however, involves the isolation of aortic receptor responses from the influences of both other sets of receptor groups and thus any inhibitory effect is not measured. The degree of cardiopulmonary inhibition upon the aortic receptor group is not clear, however, two fold increases upon carotid receptor responses have been recorded as a result of LBNP induced cardiopulmonary baroreceptor unloading (Victor and Mark, 1985). Due to the dominance of the aortic receptor function over that of the carotid in the low fit state (Shi et al, 1993a) i.e. it may be considered 'stronger', the effect of cardiopulmonary inhibition upon the aortic reflex may be less than the effect upon carotid for less fit subjects. The aortic baroreflex contribution to total arterial baroreflex gain in the highly fit state appears to be less than that of carotid. With this points in mind Fig 5.3b has been produced assuming a modest 30% reduction of the far right aortic reflex value and a modest 40% reduction of those values associated with the greatest cardiopulmonary gains (low $\dot{V}O_2max$ values) as estimates of how the aortic baroreflex gain/$\dot{V}O_2max$ relationship might appear accounting for cardiopulmonary baroreflex tonic influence.

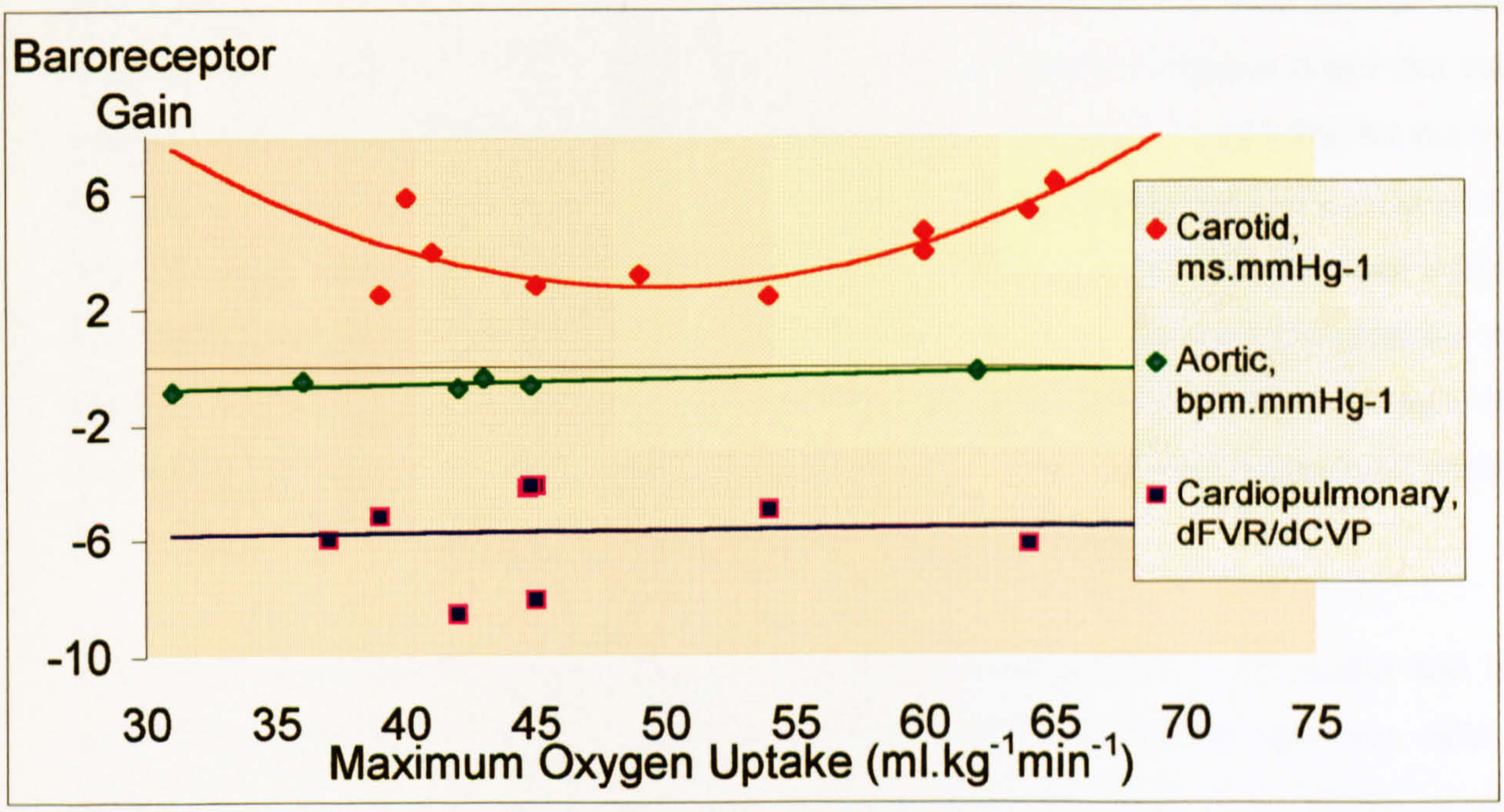

FIGURE 5.3b AMENDED BARORECEPTOR GROUP GAIN / MAXIMUM OXYGEN UPTAKE RELATIONSHIP. The aortic gain/$\dot{V}O_2$max relationship slope appears less steep when the influence of tonic cardiopulmonary baroreflex inhibition is accounted for.

Examination of the progressive LBNP results from this study shows that the carotid baroreflex gain in the trained state should have increased heart rate by 14 bpm for the 43.8 mmHg drop in systolic pressure noted at pre-syncope[17] i.e. 43% of the +32 bpm tachycardia observed during LBNP. The carotid baroreflex gain in the detrained state, however, equates to a 7 bpm increase in heart rate for the 46.3 mmHg drop in pressure[18] which equates to an 18% contribution to the total tachycardia of +39 bpm recorded. Consequently, the LBNP induced tachycardia in the detrained state would have been 7 bpm less (the difference between the +14 bpm and +7 bpm resulting from the relative carotid baroreflex gains) if the carotid baroreflex was the only mechanism affected by the reduction in fitness i.e. the tachycardia in the detrained state would have been 32 – 7 = +25 bpm. The detrained state, however, actually resulted in an additional 7 bpm during LBNP i.e. an augmented tachycardia of 39 bpm. The indication, therefore, is that other mechanisms not only offset the potential detriment of the reduced carotid baroreflex gain of the detrained state, but actively increased the heart rate response.

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[17] ((5.44 ms.mmHg^{-1} x 43.8 mmHg)/1000) x 60 bpm
[18] ((2.46 ms.mmHg^{-1} x 46.3 mmHg)/1000) x 60 bpm

The relative contributions of aortic and carotid reflex function to the total arterial reflex response was examined by Shi and co-workers (1993a). These investigators found that their estimation of aortic baroreflex gain and carotid baroreflex measures showed that for the low fit state a ratio of 6.5:3.5 respectively existed, whereas for the highly fit state a ratio of 4:6 was observed. Shi and colleagues also showed that for the highly fit state the total arterial baroreflex gain was 65% less than that of the low fit. Assuming a linear continuum for the change in ratio of contribution and magnitude of gain from low fit to high fit state, the moderately fit state should offer an aortic/carotid ratio of 5.5:4.5 and provide a total arterial baroreflex gain in the region of 32% less than that of the low fit state.

The estimated relationships derived from the measured reflex gains of 12 studies and the results from this study, therefore, indicate that the moderately trained state may offer a greater total arterial reflex response to that of the highly trained state and a slightly greater cardiopulmonary baroreflex gain, but that the untrained state provides the greatest arterial and cardiopulmonary baroreflex gains.

5.4 STRENGTH OF RELATIONSHIPS. If endurance training induced physiological adaptations or fitness itself were linearly related to orthostatic tolerance the issue might have been resolved a number of years ago. Levine's 1993 parabola model, if correct, suggests a quadratic relationship derived from the interaction of a number of variables. Levine and co-workers (1991) in summarising their investigation of mechanisms of orthostatic tolerance related to physical fitness concluded that tolerance depends on complex interactions among functional characteristics both related and unrelated to fitness or exercise training. Researchers investigating the integrated effects of variables on orthostatic tolerance by means of multiple regression analysis have found that significant predictors of tolerance were orthostatic stress induced changes in; blood volume (Levine et al., 1991; Stevens et al., 1992; Convertino, 1993), cardiac output (Convertino, 1993), stroke volume (Levine et al., 1991) and peripheral vascular resistance (Stevens et al., 1992; Convertino, 1993). When examining the relationships between variables for all subjects as a continuum (untrained, moderately trained and highly trained) in the present study, significant relationships were found between time to pre-syncope and; blood volume ($r = -0.51$, $df = 20$, $p = 0.01$), mean and diastolic arterial pressure ($r = -0.37$, $df = 20$, $p = 0.047$ and $r = -0.39$, $df = 20$, $p = 0.041$),

cardiopulmonary baroreflex sensitivity ($r = -0.38$, $df = 20$, $p = 0.045$) and resting forearm vascular resistance ($r = -0.58$, $df = 20$, $p = 0.003$). A subsequent multiple regression analysis, however, revealed that only forearm vascular resistance reasonably predicted tolerance to LBNP. This analysis gives credence to the hypothesis that endurance training is associated with decreased baseline sympathetic and heightened basal parasympathetic activity and that the improvement of orthostatic tolerance in the detrained state may have been in part due to a return to more normal vagal/sympathetic efferent activity subsequent to an improved vasomotor capability.

5.5 SUMMARY OF DISCUSSION OF INDIVIDUAL BARORECEPTOR GROUP FUNCTION

The finding that detraining induced reductions in blood volume were associated with increased tolerance to progressive LBNP, may be due to an indirect causal relationship. The possibility of increased cardiac compliance concomitant with high blood volume in the highly trained state may indicate that a detrained state could exist in which blood volume has returned to 'normal' levels but in which myocardial compliance remains high, a conjecture supported by the results of Raven and colleagues (1998) and Hickson and colleagues (1985). In this eventuality the cardiopulmonary baroreceptors could be in a state of low sensitivity[19], consequent to attenuated baroreceptor afferent discharge for any given cardiac filling. The result of this state would be heightened efferent sympathetic tone and augmented vascular resistance. The results of the present study i.e. high forearm vascular resistance, retention of high central venous pressure, increased resting heart rate and lower (albeit not significant) mean cardiopulmonary baroreceptor sensitivity in the detrained state supports this contention. This may be a transient state; as the duration of detraining continues compliance may decrease leading to an improvement of cardiopulmonary baroreflex gain in the low fit state. A transient effect of detraining therefore might result in hysterisis of the relationship between myocardial compliance and endurance fitness in that a non-linear relationship may be evident during loss of fitness but a linear relationship may exist when fitness is increased. This mechanism could explain the cardiopulmonary baroreflex gains measured for each

[19] Binomial relationships when plotted in Figs 5.3 a & b show the moderately fit state to have lower gains than the low and high fit states, however, these relationships were not significant.

fitness state and why in general training studies report a negative linear relationship between endurance fitness and cardiopulmonary baroreflex gain.

An endurance training induced heightened parasympathetic baseline may be responsible for the augmented carotid baroreflex gain measured in the highly trained state for the present study. The reduction in fitness with detraining may have returned the parasympathetic baseline towards untrained levels thus reducing parasympathetic central inhibition of sympathetic efferent traffic resulting in a decrease in carotid baroreflex gain.

A reduction in carotid baroreflex gain if acting in isolation from other elements would lead to a smaller tachycardia for the same reduction in arterial pressure during orthostasis. The finding that the tachycardic response improved highlights the fact that other factors must offset the decreased carotid baroreflex gain thus supporting the contention of Barney and co-workers (1988) and Tatro and colleagues (1992) that a change in carotid baroreflex function with change in endurance fitness does not significantly affect orthostatic tolerance.

An examination of the baroreceptor gains measured in previous work according to $\dot{V}O_2max$ provides an indication that an increase in aortic baroreflex gain with detraining to moderately fit levels, in combination with the hypothesised transient reduction of cardiopulmonary baroreflex gain, could provide the basis by which the reduction in carotid baroreflex gain is countered and a greater tachycardia response to orthostasis results. Furthermore, if the relationships proposed are correct, assumption of the findings of Shi and associates (1993a) suggests that a negative relationship may exist between overall gain and endurance fitness i.e. that sedentary subjects may have a more sensitive arterial baroreflex than the highly trained. As will be discussed, however, consideration of cardiopulmonary baroreflex inhibition of the arterial baroreflex under certain physiological conditions may have a bearing on the ultimate integrated baroreflex response.

5.6 ORTHOSTATIC TOLERANCE AND EXERCISE TRAINED STATE.

An examination of the relationship between trained state and orthostatic tolerance may be approached in two ways; firstly by assuming that the measurement of orthostatic tolerance is independent of the method employed or secondly by assuming that the method has an effect and that therefore research results should be considered according to method. The difficulty

in adopting the first approach is that a combined analysis is hindered by the different units and endpoints used. These may be divided in to four categories; cardiovascular responses to the orthostatic challenge, observance of pre-syncope or not, time to pre-syncope, and cumulative stress index. With regards to the first category a common definition of 'poor response' or 'good response' to the stress does not exist. For example Shvartz (1996) and Fortney and co-workers (1992) concluded that their trained subjects had a good response to orthostatic stress (20 min standing and LBNP) because of their lower orthostatic heart rates, whereas their untrained subjects had 'poor orthostatic tolerance' because of their greater tachycardic responses. Williamson and colleagues (1992), however, associated the attenuated heart rate response to head-up tilt of their subjects in the trained state with reduced orthostatic tolerance, a finding in agreement with the pre-syncopal heart rates measured in this study. Convertino in his 1993 review of the topic suggests that the 'effectiveness' of the blood pressure control reflex to respond to the orthostatic challenge should not be implied by these measures, but that the clearer endpoint of pre-syncope should be used to properly examine the problem. A number of studies employing head-up tilt or stand tests, however, are obliged to adopt a finite duration for the stress beyond which it is considered unethical and impractical to continue to expose the subject (Klein et al., 1980; Lansimies and Rauhala, 1986; Shvartz, 1996). For studies such as these, therefore, conclusions are derived from the attributes of 'fainters' and 'non-fainters', but without being able to define the exact tolerance of the non-fainters who are usually the majority of the subjects involved. The following discussion will therefore concentrate on the results of only those studies employing pre-syncope as an end point for all subjects expressed as time to pre-syncope or cumulative stress index and according to head-up tilt/stand tests or LBNP separately.

5.6.1 TOLERANCE TO HEAD-UP TILT AND STAND TESTS. Few studies have taken all subjects to pre-syncope using head-up tilt or stand due to the difficulties mentioned above, however, the results of three studies using time to pre-syncope, are comparable (Convertino et al., 1984; Greenleaf et al., 1988; Williamson et al., 1992). Both Greenleaf and colleagues (1988) and Williamson and co-workers (1992) found that exercise training and the exercise-trained state respectively were not associated with a change in orthostatic tolerance. Convertino and associates (1984), however, measured a significant increase in time to pre-

syncope for subjects after 8 d of cycle training. Figure 5.4 shows the mean times to pre-syncope for each subject group according to $\dot{V}O_2$max. It is of note that both Convertino and associates (1984) and Greenleaf and colleagues (1988) used 60° head-up tilt as opposed to the more commonly used 70° head-up tilt employed by Williamson and associates (1992) leading to longer head-up tilt durations for their subjects.

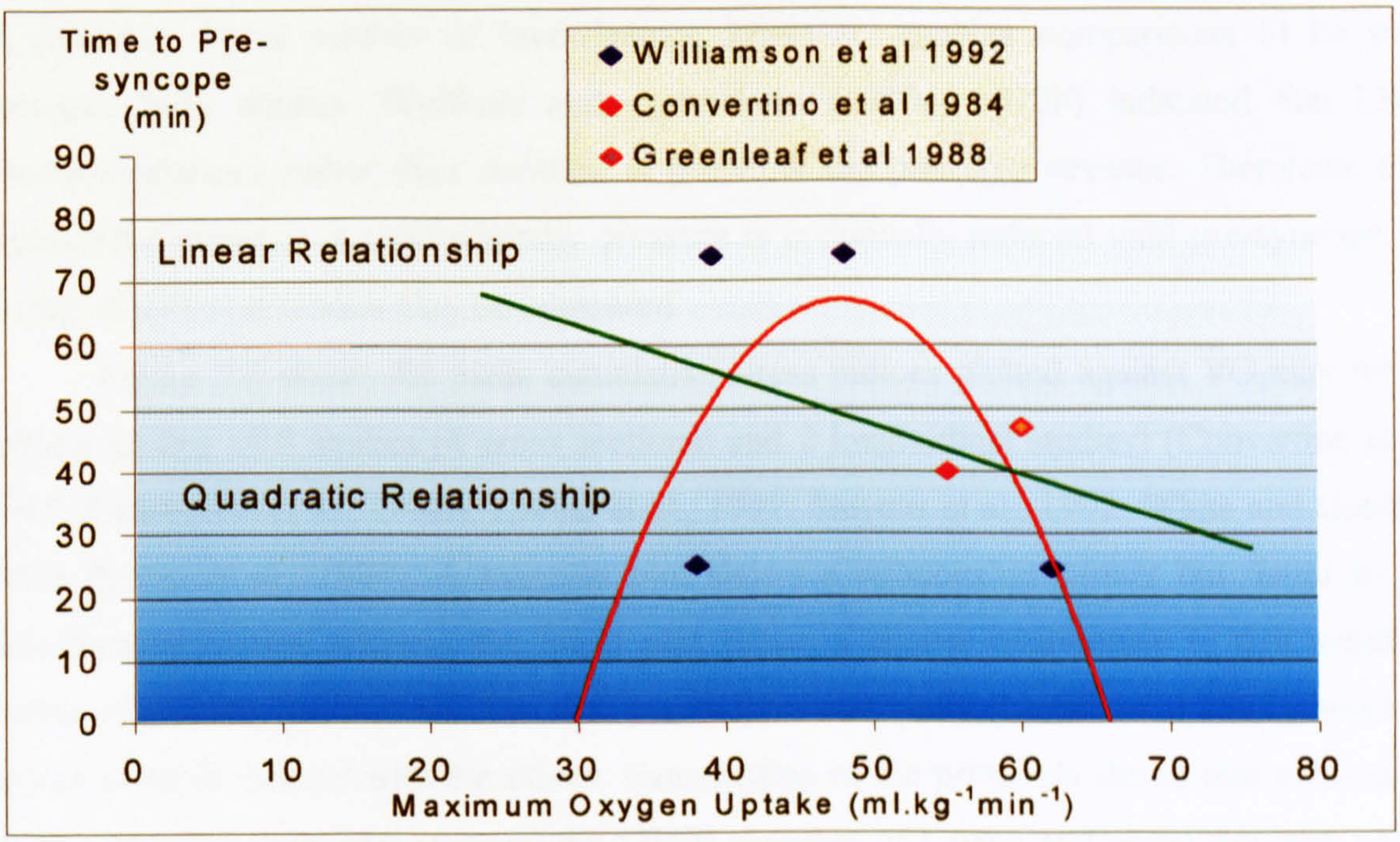

FIGURE 5.4 TOLERANCE TO HEAD-UP TILT - MAXIMUM OXYGEN UPTAKE RELATIONSHIPS DERIVED FROM THE RESULTS OF THREE STUDIES. The relationships between time to pre-syncope using head-up tilt test and $\dot{V}O_2$max derived from the results of three studies are shown. Although the possibility of type two error as a result of the use of only 6 data points must be considered too high for a valid assumption of either curve, it is of interest to note the negative linear and parabolic binomial relationships.

Although a second order polynomial plot describes a relationship similar to that proposed by Levine (1993) i.e. that increased endurance training up to a point aids orthostatic tolerance, whereas continued training beyond this threshold leads to reduced tolerance, the possibility of a type two error as a result of the use of only 6 data points must be considered too high for a valid assumption of this or the linear relationship shown.

5.6.2 TOLERANCE TO PROGRESSIVE LBNP. As discussed in the review of literature Levine's model appears to hold when the results from many previous investigations are considered singularly. An examination of the relationship using the combined results of

studies assessing 'orthostatic tolerance' by means of LBNP is made difficult, however, by the multitude of protocols employed. The principle difference between protocols is the duration/pressure profile used. Some investigators use a non-linear incremental profile e.g. – 8mmHg x 3 min, -16mmHg x 3 min, -32mmHg x 3 min, -40mmHg x 3 min, -50mmHg x 5 min (Fortney et al., 1992), whereas others use a linear profile e.g. an increase of –10 mmHg every 3 min (Lightfoot et al., 1994). The adoption of the cumulative stress index as the unit of reference by a number of investigators, however, enables comparisons to be made between these studies. Wolthuis and co-workers (1970a, 1970b) indicated that LBNP chamber pressure rather than duration is probably the principle stressor. Therefore, if an incremental protocol is used whereby pressure is continually reduced until pre-syncope, the results of different studies may be compared.

Figure 5.5 shows the mean cumulative stress indices plotted against $\dot{V}O_2max$ for the subject groups of 6 studies (4 cross sectional and 2 longitudinal studies) (Convertino et al., 1988; Convertino et al., 1990b; Levine et al., 1991; Stevens et al., 1992; White and Gotshall, 1994; Raven et al., 1998). A binomial plot shows a relationship similar but flatter to that described by Levine whereas the linear plot shows a similar relationship to that noted for studies employing head-up tilt. The data points from one study (Levine et al 1991), however, appear to be in discord with the others. Examination of the protocols shows that although all studies use an incremental protocol the LBNP chamber of Levine and associates was unable to produce pressures below -55 mmHg and thus for subjects who achieved this level a pressure of -55 mmHg was simply maintained for up to 30 min. The other 5 studies continued with incremental reductions in pressure every 2-5 min until pre-syncope was achieved. Clearly, if pressure is the crucial element of the LBNP procedure, as Wolthuis and colleagues (1970a & b) indicate, continued reductions in chamber pressure at a late stage in the protocol are likely to lead to pre-syncope earlier than the maintenance of one pressure. It is probable, therefore, that the disparate results of Levine and co-workers (1991) are as a result of the final continuous pressure stage used and should not, therefore, be used in the comparison.

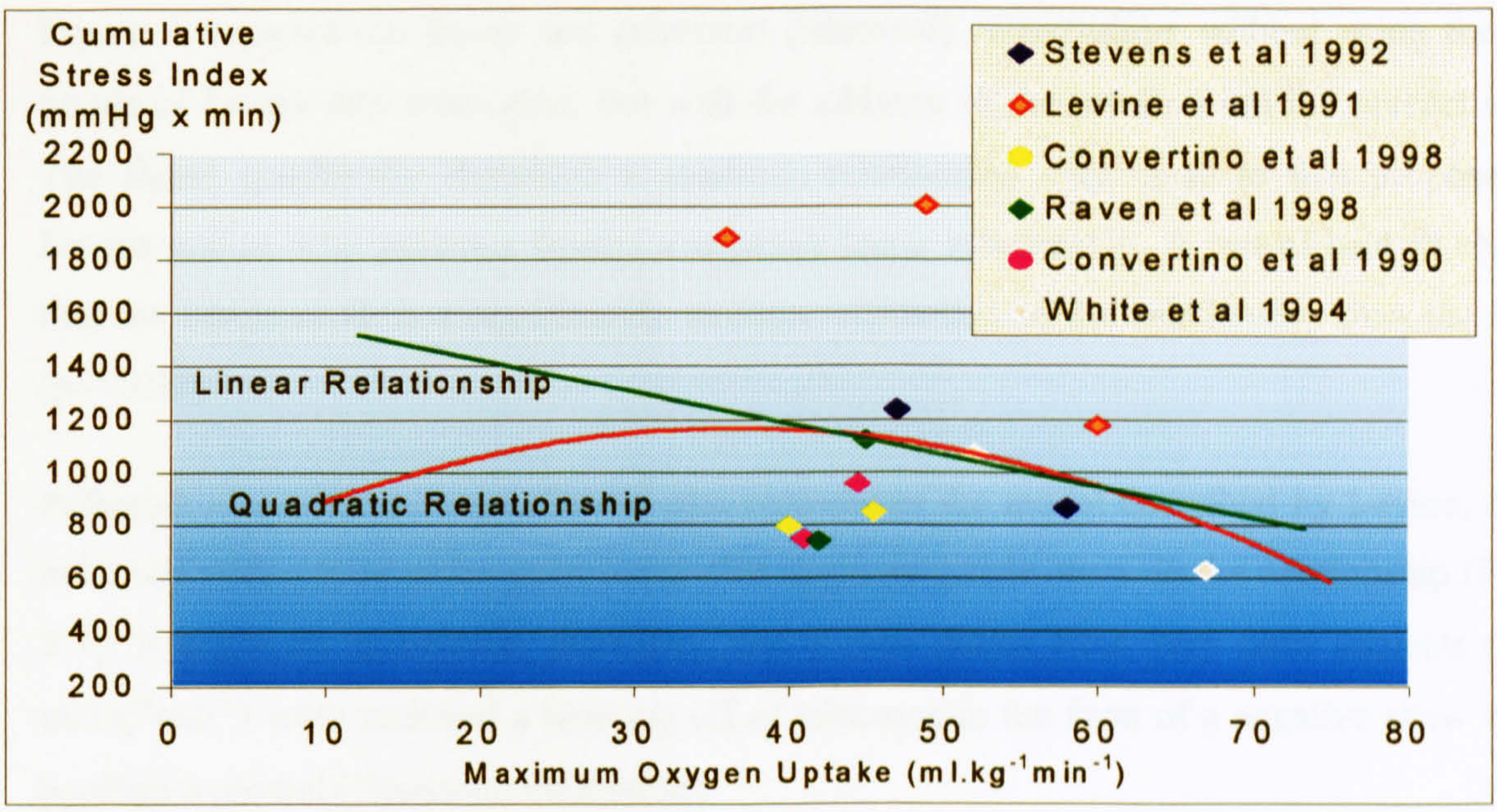

FIGURE 5.5 RELATIONSHIP BETWEEN TOLERANCE TO LOWER BODY NEGATIVE PRESSURE AND MAXIMUM OXYGEN UPTAKE. The binomial plot shows a possible quadratic relationship between cumulative stress index derived from progressive LBNP and $\dot{V}O_2max$, however, the data points of Levine et al (1991) appear to be in discord to those of the other studies.

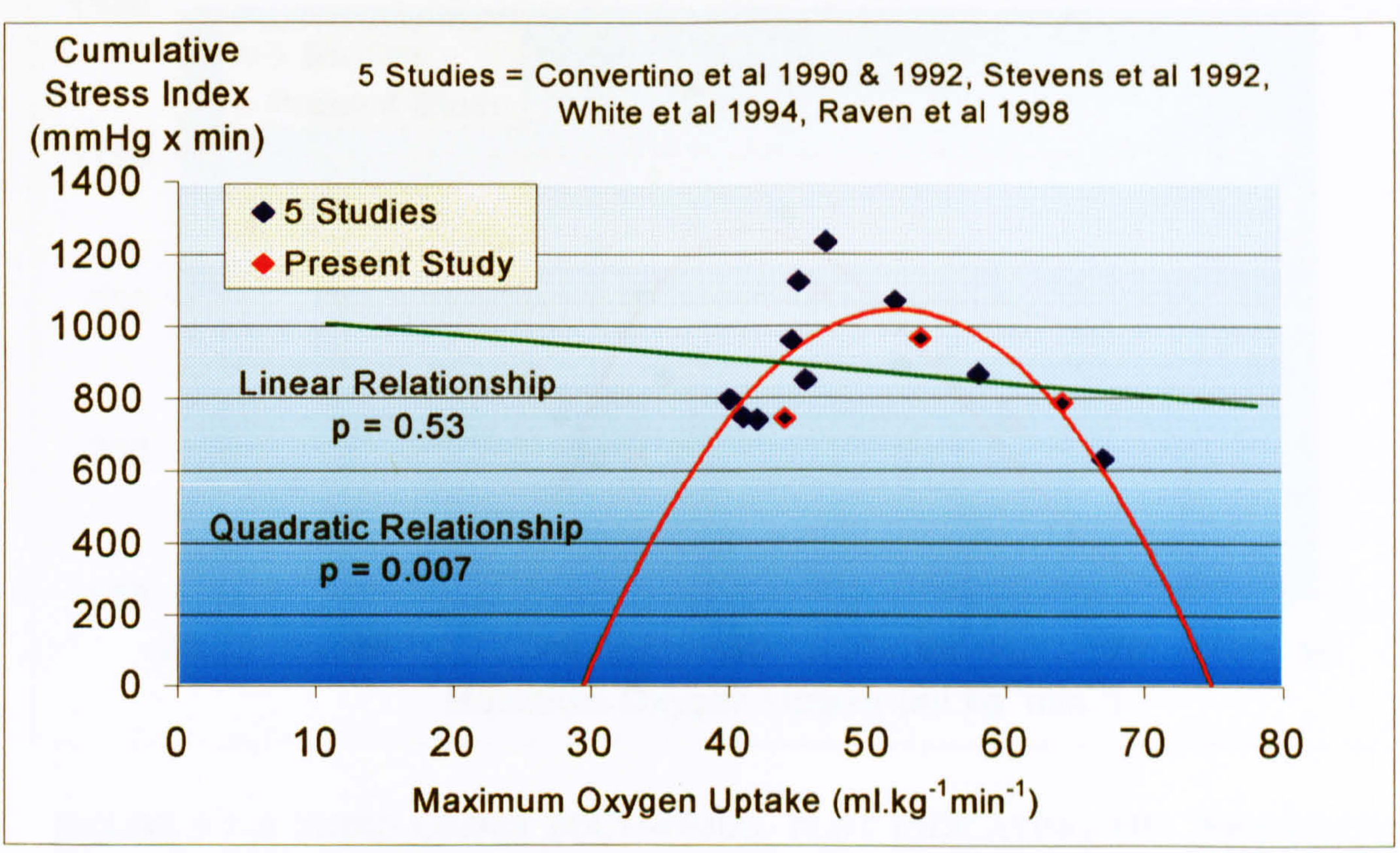

FIGURE 5.6 RELATIONSHIP BETWEEN TOLERANCE TO LOWER BODY NEGATIVE PRESSURE AND MAXIMUM OXYGEN UPTAKE. Without the data from Levine et al (1991) a test of best fit showed that the binomial plot is a significantly stronger estimation of the relationship than the linear ($p = 0.02$).

Figure 5.6 shows the linear and quadratic (binomial) relationships without using the data points of Levine and colleagues, but with the addition of the results from the present study. The figure graphically illustrates a quadratic relationship very close to that proposed by Levine and as with previous figures a negative linear relationship. A test of best fit showed that the binomial fit is a significantly stronger estimation of the relationship than the linear ($p = 0.02$).

Although a second order polynomial plot reproduces the model described by Levine, the fit achieved with a third order polynomial plot suggests a right skew in the relationship (Figure 5.7). It might be speculated, therefore, that if data points from very unfit subjects (< 35 $ml.kg^{-1}min^{-1}$) were included a tapering off of tolerance in the form of a negative skew would produce a normal (Gaussian) distribution.

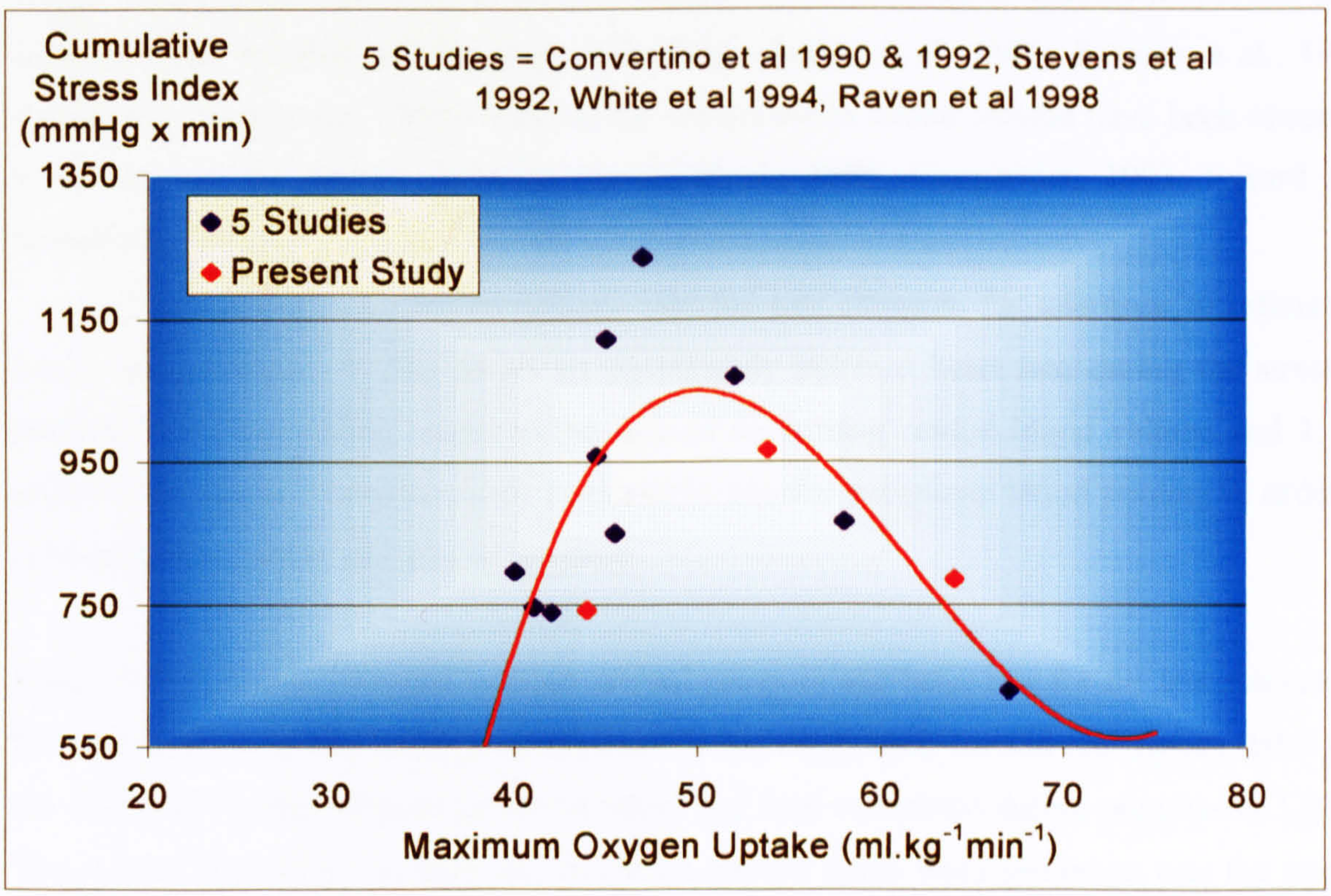

FIGURE 5.7 A THIRD ORDER POLYNOMIAL PLOT INDICATING THE POSSIBILITY OF A POSITIVELY SKEWED RELATIONSHIP BETWEEN TOLERANCE TO LBNP AND MAXIMUM OXYGEN UPTAKE.

5.7 CARDIOVASCULAR RESPONSES TO ORTHOSTATIC STRESS.

If the relationship between endurance training and orthostatic tolerance is correctly described by a parabola then the adaptations associated with training must prove advantageous to orthostatic stress initially, but disadvantage the athlete if training continues beyond a certain point. One approach to the analysis of the results of the present study is to consider the control, detrained and trained data as a single continuum i.e. untrained, moderately trained and highly trained respectively.

Orthostatic tolerance has been associated with a greater ability to increase heart rate and systemic peripheral resistance consequent to a more effective maintenance of arterial pressure (Sather et al., 1986; Convertino, 1993; Savard and Stonehouse, 1995; Shvartz, 1996). During progressive LBNP little difference in the reduction of cardiac output has been noted between tolerant and intolerant individuals (Sather et al., 1986; Stevens et al., 1992; Savard and Stonehouse, 1995) whereas the reductions in stroke volume have been observed to be less in the tolerant subjects (Sather et al., 1986; Convertino, 1993; Savard and Stonehouse, 1995).

These findings appear to indicate that the key elements for tolerance to orthostatic stress are potentially 1. The ability to significantly increase heart rate during the stress in order to maintain cardiac output in the face of decreasing central blood volume and 2. An effective peripheral vasoconstrictor response to counter peripheral blood pooling in order to protect stroke volume and arterial pressure.

Figure 5.8 shows the changes in mean arterial pressure and heart rate for the test subjects of the present study in the highly trained (trained) and moderately trained (detrained) states and the untrained control subjects (mean of initial and final measures) during progressive LBNP. The resting heart rates for high and moderate trained states were similar as was the rate of increase during LBNP. In the moderately trained state, however, heart rate rose to a greater degree before pre-syncope was reached. Resting heart rate was greatest for the untrained control subjects and the rate of rise and maximum level achieved were both greater than those of the test subjects for either trained state. During LBNP mean arterial pressure was

maintained in the moderately trained state, elevated in the untrained state, but decreased slightly in the highly trained state. The magnitude of the reductions of arterial pressure and heart rates at pre-syncope were similar for all states except that the untrained subjects' heart rate dropped slightly farther, but remained higher than those measured for either of the trained states.

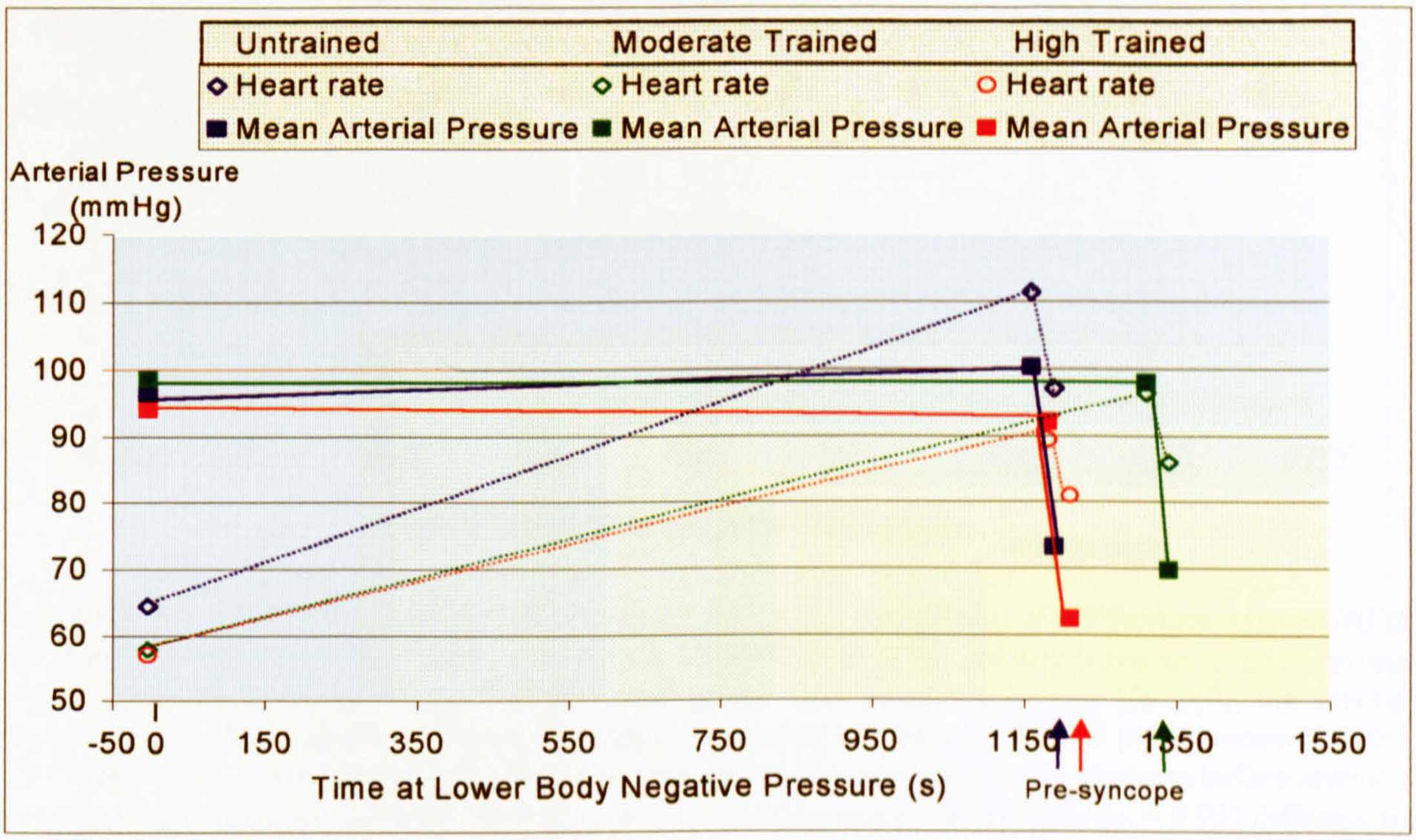

FIGURE 5.8 ABSOLUTE MEAN ARTERIAL PRESSURE AND HEART RATE MEASURED DURING PROGRESSIVE LBNP FOR EACH TRAINED STATE. All measures were taken in the right lateral decubitus position. The first data points (far left) were measured at rest, the second points were the maximal or minimum values measured immediately before pre-syncope and the third data point in each case (far right) is the minimum value recorded at pre-syncope before ambient chamber pressure was restored. All pre-syncope measures were significantly ($p < 0.05$) different to resting values.

Fig 5.9 shows the systolic and diastolic arterial pressure changes during progressive LBNP. During LBNP diastolic pressure rose slowly for each trained state reaching a level approximately 5 mmHg greater than at rest by the point of pre-syncope. Systolic pressure was well maintained until pre-syncope by the untrained and moderately trained groups, but progressively decreased throughout in the highly trained state. At pre-syncope the magnitude of the systolic and diastolic pressure reductions was similar for all states, however, in the highly trained state both arterial pressure variables dropped to a lower level than those of the moderate and untrained states.

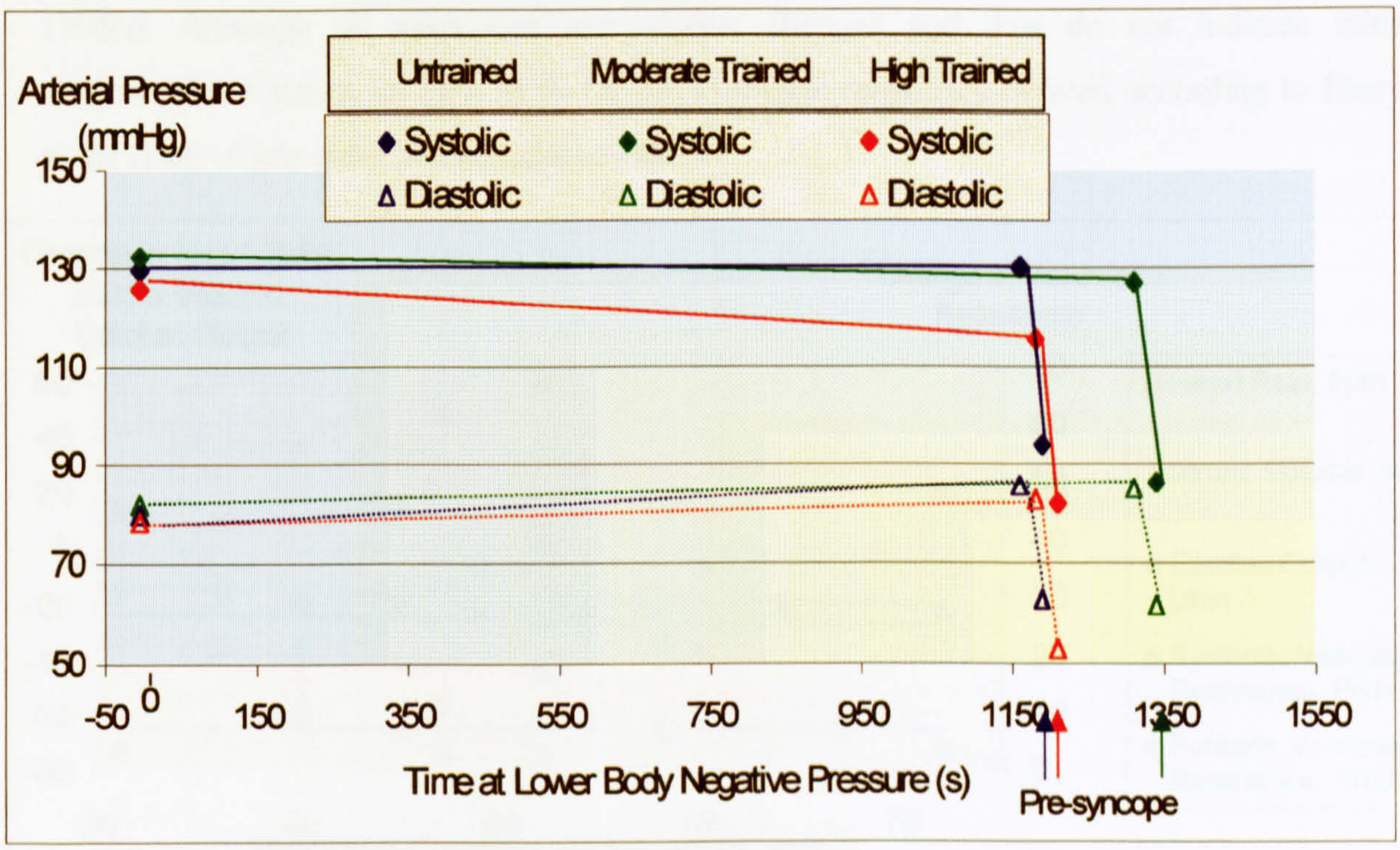

FIGURE 5.9 ABSOLUTE SYSTOLIC AND DIASTOLIC ARTERIAL PRESSURES MEASURED DURING PROGRESSIVE LBNP FOR EACH TRAINED STATE. All measures were taken in the right lateral decubitus position. The first data points were measured at rest (far left), the second points were the maximum or minimum values measured immediately before pre-syncope and the third data point (far right) in each case is the minimum value recorded at pre-syncope before ambient chamber pressure was restored. All pre-syncope measures were significantly ($p < 0.05$) different to resting values.

The principle differences between the responses for the three trained states, therefore, were that the heart rate elevations seen during LBNP were greater in the moderate and untrained states than the high trained and systolic and mean arterial pressures progressively dropped during LBNP in the highly trained state but not for the other states. Consequently, at the point of pre-syncope 1. Heart rate and arterial pressures were lower in the highly trained state than for the other states, 2. Heart rate was significantly higher in the untrained state than for the other states, 3. The duration of heart rate increase in the moderately trained state was greater than for the other states and 4. Diastolic pressure continued to increase in the moderately trained state beyond that of the other states.

Figures 5.10 and 5.11 show the mean cardiovascular responses to orthostatic challenges according to trained state recorded in 6 studies (Levine et al., 1991; Fortney et al., 1992;

Stevens et al., 1992; White and Gotshall, 1994; Savard and Stonehouse, 1995; Convertino, 1998b). Although all responses are relative changes and thus do not indicate initial cardiovascular states, an idea as to the physiological responses derived according to fitness at the point of pre-syncope can be ascertained.

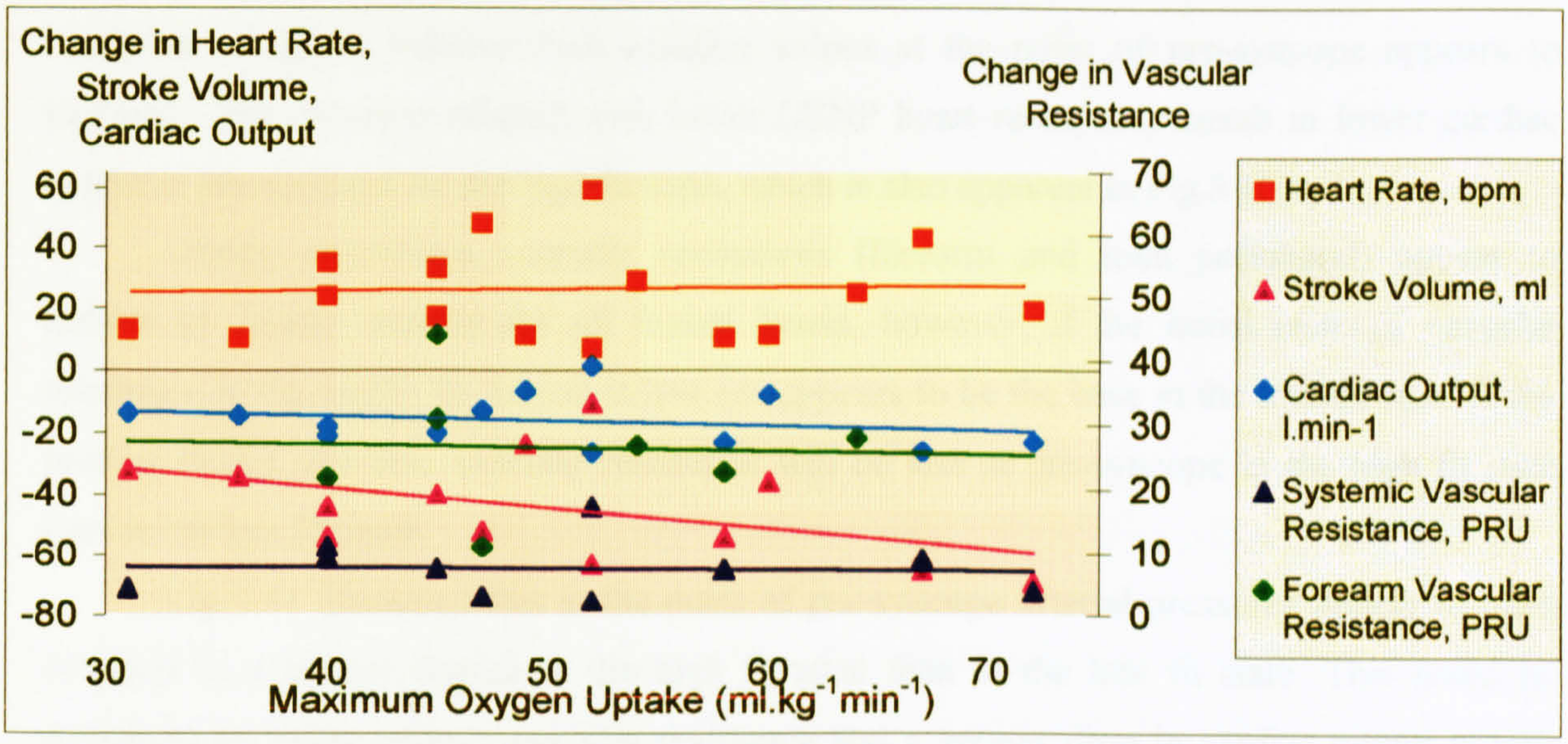

FIGURE 5.10 CARDIOVASCULAR RESPONSES (AT PRE-SYNCOPE) TO ORTHOSTATIC HYPOTENSION VS MAXIMUM OXYGEN UPTAKE. The mean cardiovascular responses to orthostatic challenges measured at or immediately before pre-syncope according to trained state recorded by 6 studies. Changes from resting values in units as shown.

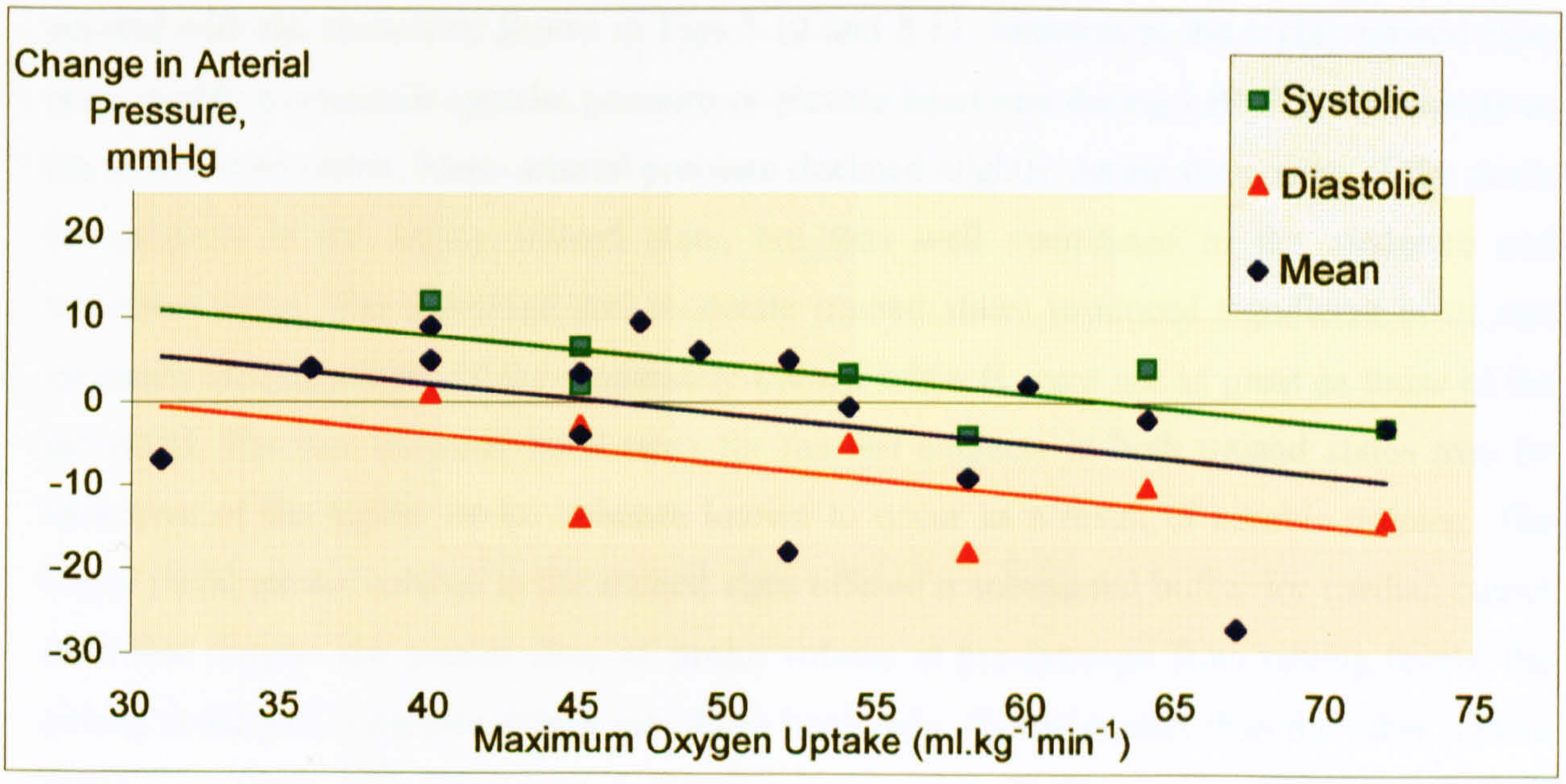

FIGURE 5.11 ARTERIAL PRESSURE RESPONSES (AT PRE-SYNCOPE) TO ORTHOSTATIC HYPOTENSION VS MAXIMUM OXYGEN UPTAKE FROM 6 STUDIES. Each data point shows the mean response measured at or immediately before pre-syncope for a subject group with a mean $\dot{V}O_2max$ as indicated by the abscissa. Changes from resting values.

Fig 5.10 appears to show that at pre-syncope heart rate is elevated from baseline levels by a similar magnitude for all levels of fitness. Clearly as high fit subjects have slower resting heart rates than their less fit counterparts, at pre-syncope absolute heart rate will not be as high as that of someone less fit. With increased aerobic fitness the magnitude of the reduction of stroke volume from baseline values at the point of pre-syncope appears to increase. This, when combined with lower LBNP heart rates, may result in lower cardiac output at pre-syncope for the high fit state, which is also apparent in Fig 5.10.

During orthostasis vascular resistances (forearm and total peripheral) appear to reduce by similar amount for all fitness levels, however, if the initial state of vascular resistance in the highly fit subject is low (as appears to be the case in the trained state in the present study), absolute vascular resistance will be less at pre-syncope in the high fit state than in the less fit states.

Fig 5.11 illustrates that at the point of pre-syncope arterial pressures appear to have dropped to a greater degree in the high fit state than in the less fit state. This could be explained by lower relative vascular resistance and a greater drop in cardiac output at pre-syncope for the highly fit state.

The cardiovascular responses to progressive LBNP measured in the present study agree in general with the responses shown in Figs 5.10 and 5.11. Subjects in the highly trained state were unable to maintain systolic pressure or elevate heart rate during LBNP as effectively as the less trained states. Mean arterial pressure declined slightly during the course of the stress for subjects in the highly trained state, but was well maintained in the moderate and untrained states. The untrained and moderate trained states produced significant heart rate increases although those of the moderately trained subjects were not as great as those of the untrained. The less elevated heart rates for the test subjects in both trained states may be indicative of the higher stroke volumes known to occur as a result of aerobic training. The larger initial stroke volume in the trained state offered a substantial buffer for cardiac output such that despite the greater drop in stroke volume at pre-syncope from resting levels, the overall reduction in cardiac output may have been only slightly greater than the other trained states.

5.7.1 COMPARISON OF MODERATE AND HIGHLY TRAINED RESPONSES

When considering only the moderately and highly trained states the conclusions drawn from the responses shown in Figs 5.8 and 5.9 appear valid in that insufficient tachycardia and an inadequate maintenance of arterial pressure were associated with the poorer tolerance to LBNP in the trained state. The significantly lower forearm vascular resistances measured during mild LBNP may indicate an attenuated vasoconstrictor response when the test subjects were highly trained. The potential aid to the maintenance of cardiac output provided by greater blood and stroke volumes and central venous pressure in the trained state may have been insufficient to counter what could have been a significantly attenuated ability to increase vascular resistance during orthostasis.

5.7.2 COMPARISON OF UNTRAINED AND MODERATELY TRAINED RESPONSES

The responses of the untrained subjects and test subjects in the moderately trained state similar and yet a clear difference in tolerance was apparent. The small cardiovascular differences observed were slightly higher initial arterial pressures and lower heart rates for the moderately trained state and a greater rate of heart rate rise during LBNP for the untrained subjects. The advantage of training induced hypervolaemia was not present due to the reduction of blood volume to control levels during detraining. The greater forearm vascular resistance and arterial and venous pressures measured, however, appear to indicate a generally greater level of systemic vascular resistance in the moderately trained state than the untrained. This augmented vasomotor capability may have enabled the detrained test subjects to moderate the tendency for LBNP to reduce cardiac filling and stroke volume which in combination with the detrained state's moderately sensitive baroreflex control of heart rate enabled cardiac output to be maintained for longer.

If a heightened level of baseline vagal activity derived from endurance training was the single or most significant factor directly involved in the relationship between orthostatic tolerance and endurance fitness, a linear reduction between tolerance to LBNP and endurance fitness ($\dot{V}O_2max$) would probably be apparent. It may be that this mechanism is the principle element in the reduction of tolerance when endurance fitness exceeds the

moderate level, however, other factors must offset this effect during a transition from untrained to moderately trained states.

5.8 POTENTIAL AETIOLOGY OF ENDURANCE TRAINING EFFECT UPON ORTHOSTATIC TOLERANCE.

5.8.1 CARDIAC STRUCTURE AND FUNCTION. Training induced left ventricular hypertrophy may alter the structure and function of the heart such that the cardiac pressure/volume relationship could be considered inappropriate for orthostasis (Levine, 1993; Raven et al., 1998). Levine (1993) after a comprehensive investigation of the structure and function of the heart after endurance training hypothesised that endurance training increases the capacity to utilise the Frank-Starling mechanism to aid cardiac output during exercise. The researchers observed greater left ventricular compliance in the trained state such that a two fold augmentation of change in stroke volume was possible for a given change in cardiac filling pressure[20], a capability which can be considered beneficial during intense exercise but disadvantageous during orthostasis.

Estimations of aortic and cardiac compliance suggest that endurance training results in an increase in myocardial and possibly arterial compliance (Shi et al., 1992; Levine, 1993). 'Remodeling' of the cardiac and arterial tissue may enable the cardiac chambers and aortic walls to expand more easily thus accommodating the training induced expansion of blood volume and cardiac output (Raven et al., 1998). In addition to potentially altering the pressure/volume relationship of the heart, the reduction of visco-elastic coupling of the cardiac and aortic baroreceptors resulting from increased compliance may have lead to increased elasticity of the receptors which would consequently require greater changes in vascular and myocardial stretch for receptor activation than in the untrained state. Such a mechanism could explain the reduced cardiopulmonary and aortic baroreceptor sensitivities generally observed in endurance athletes if only major arteries close to the heart are affected i.e. the more distant carotid baroreceptors may not be affected in the same manner as a result of their locale.

5.8.2 BAROREFLEX FUNCTION. The consensus, with which the results of the present study are in general accord, is that cardiopulmonary (and aortic) baroreflex sensitivity

decreases and carotid gain increases with increased endurance fitness. If the view that cardiopulmonary receptor activity imposes a tonic inhibitory influence upon that of arterial baroreflex function is accepted and that the relationships shown in Fig 5.3b are reasonable the untrained state offers highly sensitive aortic, carotid and cardiopulmonary baroreflexes, the combination of which provides a high degree of reflex buffering capability. In the moderately trained state the subject possesses lower baroreceptor gains with the result that the combined arterial baroreflex is less sensitive than that of the untrained state, but may be more sensitive than that of the highly trained state. The highly trained state appears to offer a combined arterial baroreflex which is less sensitive than lesser trained states despite an augmented carotid baroreflex in addition to the least sensitive cardiopulmonary baroreflex and consequently indicates the least effective overall baroreflex state.

5.8.3 NEUROENDOCRINE MECHANISMS. The principle neuroendocrine aid to the maintenance of vascular resistance and subsequent regulation of arterial pressure during orthostasis is angiotensin-mediated vasoconstriction via sympathetic stimulation of renin release by the kidney. Unloading of the cardiopulmonary and arterial baroreceptors results in augmented PRA and AVP mediated vasoconstriction, anti-diuresis and heightened vascular tone. The results of the present study show that greater reductions in pulse and mean arterial pressures occurred during LBNP for the test subjects in the trained state. The reduction in sino-aortic baroreceptor stimulation might be expected to result in a more profound renin-angiotensin and AVP response than for the lesser-trained conditions, thus aiding LBNP tolerance. The relative tolerances observed, however, do not support this contention. This might be explained by means of the earlier examination of baroreflex gains relative to $\dot{V}O_2max$, which indicated that the highly trained condition may be associated with the least sensitive total arterial baroreflex. This being so, the response of the arterial baroreceptors overall to reduced pulse pressure in the trained state could prove no better or even worse than that of the lesser trained states despite a higher carotid baroreflex gain. The trained state, therefore, may be associated with sub-optimal PRA and AVP secretion due to less responsive arterial baroreceptors. The fitness related alteration in central integration of afferent baroreceptor traffic, therefore, is probably directly involved with the relationship between orthostatic tolerance and endurance fitness not only through its direct effect on heart

[20] Ascertained by means of pulmonary capillary wedge pressure.

rate and vascular resistance but also by means of hormonal control of blood volume and vascular resistance.

Endurance training induced increases in basal parasympathetic activity concomitant with reduced efferent sympathetic activity could also explain observed attenuated plasma PRA and AVP concentrations detrimental to orthostatic tolerance. The current results, however, show that the trained state and untrained state had similar levels of tolerance to LBNP and that the moderately trained state improved tolerance. A detraining induced reduction in baseline parasympathetic activity offers the possibility of improved sympathetic vasoconstriction and neuroendocrine responses (PRA and AVP) to orthostasis over that of the trained state. This mechanism alone, however, would not provide the detrained state with a tolerance to orthostasis above that of the untrained state because it might be assumed that the moderately trained state would possess a neuroendocrine capability between that of fit and unfit states. As the maintenance of arterial pressure during orthostatic stress requires the combination of tachycardia and systematic vasoconstriction the slightly lower levels of tachycardia in the moderately trained state in the present study supports the contention that control of vascular resistance must have been more effective to enable LBNP to be tolerated longer. The measured and estimated lower baroreflex gains of the detrained test subjects compared to controls indicates that vascular control by means of baroreflex activation was probably less effective. Consequently, in the absence of a greater blood volume reserve an augmented neuroendocrine capability would provide the necessary vasoconstrictor capability. It can be speculated that the combination of retention of some training induced adaptations and loss of other adaptations may have endowed the detrained subjects with a transient state of neuroendocrine hypersensitivity possibly associated with low parasympathetic basal tone.

5.9 SUMMARY OF THE CARDIOVASCULAR RESPONSES TO AND POSSIBLE AETIOLOGY OF ENDURANCE TRAINING INDUCED CHANGES IN ORTHOSTATIC TOLERANCE

The results of the present study show that in the highly trained state heart rate and arterial pressure responses to progressive LBNP are not as great as those of the moderate and untrained states. Although the orthostasis induced tachycardia measured in the untrained

state was greater than that of the moderately trained state, arterial pressure was able to be maintained significantly longer during LBNP in the moderately trained state and thus this condition provided the greatest tolerance to orthostatic stress.

Alterations in the compliance characteristics of the heart and the visco-elastic coupling of associated baroreceptors as a result of endurance training may result in greater reductions in stroke volume for given changes in central venous pressure and decreased baroreceptor sensitivity respectively. Such a change in the pressure/volume relationship and compliance of the heart may be appropriate for regular high intensity exercise, but not for orthostasis.

The changes in individual baroreceptor group function, possibly as a result of endurance training induced changes in myocardial compliance and altered parasympathetic baseline levels, appear to combine to produce a general negative relationship between VO_2max and arterial baroreflex gain which may hinder the highly trained athlete during orthostasis. Furthermore a general reduction of baroreflex sensitivity and heightened parasympathetic activity may possibly attenuate the neuroendocrine response to orthostasis in the highly trained state. Although these conditions appear to offer the trained athlete a basis for poor orthostatic control, other training induced adaptations (for example increased blood and stroke volume and a greater heart rate reserve) appear to offset these responses to provide a condition of orthostatic tolerance equivalent to that of untrained subjects i.e. 'normal tolerance'.

The moderately trained state may derive its' improved tolerance to orthostasis from a heightened vasoconstrictor capability associated with a detraining induced reduction in parasympathetic baseline and improvement in neuroendocrine and baroreflex response over that of the highly trained state. The retention of some training induced adaptations related to vasomotor capability probably provide the detrained athlete with the ability to tolerate orthostasis beyond the levels associated with the untrained and highly trained states.

5.10 INTEGRATED BAROREFLEX FUNCTION (MICROGRAVITY RELATED DISCUSSION)

The primary finding of the microgravity element of the study was that lower baroreflex gains occurred during acute exposure to microgravity than during +1G when seated or at 6° head-

down tilt. Baroreflex function determined after moderately long exposures to microgravity (Fritsch et al., 1992; Fritsch-Yelle et al., 1994) can be expected to differ from measures obtained during this study because the time-course of parabolic microgravity and head-down tilt in these experiments was insufficient to allow chronic adaptation mechanisms to come into play. Differences in the cardiovascular changes caused by the three conditions, as opposed to differences between physiological adaptations to the conditions, are more likely to be the cause of the different BRSI values recorded.

The number and complexity of reflex responses and physiological changes that occur during and after the performance of a Valsalva's manoeuvre make analysis and inter-subject comparison difficult. Eckberg and Slight (1992) in their monograph on the human baroreflex system point out that variations in subject pre-strain lung volumes, differences in body position, individual breathing patterns, post-expiratory effort and whether or not leaks in the pressure system are used, all affect the haemodynamic responses. It should be noted, therefore, that the assessment of BRSI by means of Valsalva's manoeuvre induced physiological responses in parabolic flight has inherent difficulties and that it is possible that the gross effects of the Valsalva's manoeuvre may mask some of those produced by microgravity.

Certain difficulties derive directly from the nature of the parabolic flight environment which is such that physiological steady state does not occur during the course of a parabolic manoeuvre due to the continually changing gravity vector. The greatest changes in gravity during each flight were the transitions between +1.8G and microgravity which typically occurred over 3 to 5 s. The periods of increased acceleration to which subjects were exposed to which may have been of most importance, however, were the 20 s exposures to +1.8G immediately preceding and succeeding each period of microgravity. Glaister (1970) points out that the hydrostatic pressure gradients seen in upright humans are almost abolished when the supine position is adopted. The vertical heart to brain pressure gradient is virtually absent thus enabling much greater acceleration levels in the transverse (Gx) plane to be tolerated than is the case in the vertical plane (Gz) (Glaister, 1970). Early investigations of the effects of transverse acceleration on the human body indicate that a small degree of bradycardia (pulse rate decreasing by 5 to 20 bpm) occurs during +Gx up to 15G (Lambert et al., 1945; Duane et al., 1953). The subject examined over the course of the three flights in the present

study showed a mean 13% reduction in heart rate when supine at +1.8Gx as compared to supine at +1Gx, data in accord with that of Wood and colleagues (1960) who recorded a 4% to 16% decrease in heart rate during +2Gx. These authors also found that cardiac output was reduced by a mean of 16% during exposures to +2Gx, a finding they ascribed primarily to the associated bradycardia but also in part to reduced stroke index. Such reductions in heart rate are likely to be as a result of the small effect +Gx has upon arterial pressure (Howard, 1965). Any increase in arterial pressure would stimulate arterial baroreceptors leading to a reflex slowing of the heart. Arterial pressure measurements recorded by Wood and colleagues (1960) showed that mean aortic pressure rose progressively with increased +Gx acceleration when in the supine position. The authors also report that mean arterial pressure rose by 16% from +1Gx baselines when subjects were exposed to +2Gx and by 22% during +3.5Gx. The results of this study show a small, non-significant increase of 3.2% when subjects were exposed to +1.8Gx.

Clearly the changes in acceleration to which the subjects were exposed and the subsequent effects upon heart rate and blood pressure must be considered a limitation of this element of the study. The choice of the supine position throughout experimentation, as opposed to the upright position, however, kept these effects to a minimum. Unfortunately, the difficulties in achieving steady state measures and the possibility of Valsalva's manoeuvre responses partially masking those resulting from microgravity are unavoidable in studies using parabolic manoeuvres as a means of providing a microgravity environment and in those using the Valsalva's manoeuvre to study integrated baroreflex responses, and must therefore be born in mind when considering the results.

The ease of use of the Valsalva's manoeuvre, however, as a means of studying the integrated baroreflex response in man is such that it is a highly practical method to employ in the parabolic flight environment. The manoeuvre and response can be initiated and concluded in 20 s thus enabling its performance during the microgravity period of a single parabola. Although the nature of the human baroreflex dictates that the assessment of responses to a number of Valsalva's manoeuvres is required in order to ascertain a representative measure of baroreflex function, one parabolic flight typically consists of 30+ parabolas and therefore enables repeated measures to be made. Furthermore, the measurement of mouth pressure during the Valsalva's manoeuvre provides an excellent estimation of intra-pleural pressure

change and thus allows a consistent, easily quantifiable and reproducible means of changing cardiac variables and arterial pressure. Therefore, providing variables such as pre Valsalva's manoeuvre inspiration, expiratory leak and body position are controlled, a number of manoeuvres can be performed using identical primary physiological stimulus, allowing a mean index of baroreflex to be derived from the responses.

Although the primary stimulus applied can be consistent between subjects, the variability of the response has lead to differences in opinion as to the correct method of analysis. Some investigators have used the second or third succeeding R-R interval for the analysis of BRSI, to allow sufficient time for the lag between physiological stimulus (change in systolic pressure) and effect (change in R-R interval) to occur (Palmero et al., 1981; Smith et al., 1987). The choice of interval to associate with systolic pressure may be dictated to some degree by the range of phase IV pulse intervals included for analysis (Smith et al., 1987). A preliminary investigation of the relationships between systolic pressure and various succeeding R-R intervals for the present study showed a significantly stronger correlation between systolic pressure and the first R-R interval than for the second or third succeeding intervals. Pickering and Davies (1973) conducted a similar examination and reported that the same or following interval in which the pulse wave occurs showed the strongest correlation with systolic pressure.

The R – P intervals associated with the pulse waves used for analysis in the present study ranged from 470 ms to 780 ms. Data from the analysis of carotid sinus stimulation and the resulting R – R interval prolongation showed that in 80% of subjects a response occurred during the R – R interval in which the stimulus was applied (Evetts 1997, unpublished data). The application of the stimulus during this analysis was timed to occur 750 ms before the next anticipated P wave (Eckberg, 1976). These findings suggest that the lag between arterial baroreceptor stimulus and cardiac slowing is less than 800 ms, a contention supported by Eckberg (1976) who reported reflex latencies of 250 to 300 ms. The indications are, therefore, that reflex alterations in R-R interval are sufficiently rapid to show an effect before the ensuing systolic contraction if the stimulus occurs early in the R – P interval, or during the next diastole if the stimulus was provided in the latter part of the interval. Thus in the present study the systolic pressures during phase IV of the Valsalva's manoeuvre were correlated with the R - R interval immediately following each R wave.

A cephalad fluid shift on entry to a microgravity environment greater than that observed when moving to 6° head-down tilt (Thornton et al., 1992), should this happen, could explain some of the results of this study. The 3 to 5 s transition from +1.8G to microgravity combined with the 3 s count down to the start of the Valsalva's manoeuvre allows a large amount of the associated blood volume redistribution to occur prior to the expiratory effort (Buckey et al., 1996a; Foldager et al., 1996). Blood volume redistribution to the thorax increases stimulation of the cardiopulmonary receptors thus augmenting any inhibitory influence they have upon arterial baroreflex control of blood pressure during Valsalva's manoeuvre. At +1G during phase II of the Valsalva's manoeuvre reduced venous return and a subsequent drop in arterial pulse pressure leads to a reduction in arterial receptor afferent discharge and thus augmentation of efferent sympathetic activity which leads to an increase in vascular tone and heart rate. During microgravity, inhibition of this reflex by cardiopulmonary receptor function would restrict this response and thus lead to a reduced arteriolar vascular constriction and cardiac filling. Consequently, mean arterial pressure and pulse pressure would not increase to the extent seen in the head-down tilt position. Although phase II mean arterial pressures were not significantly different between conditions, the microgravity values tended to be less than head-down tilt values, furthermore a significantly smaller mean pulse pressure was noted during microgravity in the data from the first campaign than that observed when at head-down tilt. Therefore, when considering the integrated efferent activity during phase II, the arterial receptor contribution may be diminished as a result of inhibition by cardiopulmonary baroreceptor activity. In addition it is also likely that a reduction in the arterial baroreceptor contribution to the integrated response occurs as a direct result of the reduced pulse pressure during microgravity.

During microgravity the inhibition of arterial receptor efferent activity, should this indeed occur, would continue on cessation of the Valsalva's manoeuvre expiratory effort as a result of the cephalad movement of blood stimulating cardiopulmonary receptors. A continued inhibition in this manner would lead to less heart rate slowing and vascular dilatation during phase IV than would occur at 1G, i.e. arterial pressure would not decrease as rapidly as in 1G. The result would be, as seen during microgravity for both campaigns, a large phase IV arterial pressure overshoot as returning blood is ejected into constricted vascular beds. The significantly greater microgravity phase II to phase IV arterial pressure change recorded in this study may have been accomplished by a non-significant trend

towards lower phase II pressures and higher phase IV pressures in microgravity, observations which fit well with the above postulate. In this manner mean arterial pressures in +1G and microgravity may be similar but the changes of arterial pressure between Valsalva's manoeuvre phases may be significantly greater in the microgravity environment than that seen at +1G.

An inhibition of aortic baroreflex control of heart rate would not cause the greater tachycardia seen during Valsalva's manoeuvre phase II when weightless, but could partially explain the reduced reflex gain derived from phase IV. It can be hypothesised that during the phase II reduction in cardiac filling any inhibitory influence normally derived from a microgravity augmented filling would be reduced, possibly to the extent that there would be little effect on heart rate. During phase IV, however, a combination of increased central volume due to microgravity and post strain venous return could result in a large effect and thus a measurable difference in the control of heart rate.

Any plausible explanation based on a negative interaction of cardiopulmonary/arterial receptor function during an acute augmentation of central volume, is invalid if central venous pressure falls during microgravity, as appears to be the case, leading to reduced cardiopulmonary receptor stimulation. The observation of reduced central venous pressure in space (Blomqvist, 1996), if not the result of hypovolaemia, suggests that either central blood volume change is in fact less than that produced by 6° head-down tilt, or that the ground based 'central venous pressure/heart volume' relationship is altered. Data have not been produced to indicate a smaller fluid shift in microgravity than that observed during 6° head-down tilt and, with the exception of central venous pressure and despite very little supporting research, the physiological effects of both so far have been assumed to be similar (Kakurin et al., 1976; Tomaselli et al., 1987; Schaffer-Bailey et al., 1996).

Increases in left ventricular volume have been recorded within 24 hr of a sojourn in orbit (Buckey et al., 1996a; Norsk, 1996) and within 25 s on exposure to microgravity (Johns et al., 1994) despite reductions in central venous pressure (Blomqvist, 1996; Buckey et al., 1996a). The possibility of microgravity reducing tissue and organ pressure upon the heart has been suggested as one mechanism by which the normal 'central venous pressure/heart chamber volume' relationship is changed (Blomqvist, 1996; Buckey et al., 1996a). Such

reductions of extra-cardiac pressure might occur in conjunction with decreases in peripheral extra-vascular tissue pressure and thus act to increase cardiac and vascular transmural pressures (Shepherd and Abboud, 1983; Buckey et al., 1996b). Buda and co-workers (1979) reduced intrathoracic pressure at +1G in human subjects using the Müller manoeuvre. Their observations that left ventricular end diastolic and end systolic volumes increased concomitant with a reduced left ventricular ejection fraction despite increased right ventricular filling, suggested an increase in ventricular transmural pressure. Such findings at 1G support the contention that a similar mechanism may occur during microgravity.

A significant positive correlation between central venous pressure and $+G_x$ acceleration is evident in the supine position (Blomqvist, 1996). Paiva and colleagues (1989) propose that when supine at +1G intra-abdominal positive pressure acts on the lower ribcage to overcome the direct expiratory effect of $+G_x$, producing an opposing inspiratory effect. If $+G_x$ is reduced abdominal transmural pressure may increase raising abdominal compartment pressure in the vertical plane (as intra-abdominal pressure equilibrates) contributing to the opposition of expiratory effort. Consequently, when entering microgravity in the supine position it is conceivable that the gravitational unloading of the anterior rib cage reduces pressure upon the thoracic cavity which, when combined with the inspiratory effect of the abdominal compartment, reduces intrapleural, tissue and organ pressure and central venous pressure,

If decreased tissue and organ pressures on the heart lead to raised cardiac transmural pressure, as Buda and co-workers (1979) hypothesise, then heart chamber pressures may decrease as the heart walls are 'pulled out', without an associated change in blood volume. This mechanism could explain an augmentation of central blood volume concomitant with a minimal increase or even a decrease in central venous pressure on entry to microgravity. If increased stretch of the cardiac receptors in this manner was greater than that found at the carotid sinus a larger contribution to the integrated baroreflex response than that seen at 1G may derive from the cardiopulmonary receptors. Should additional inhibition of the arterial baroreflex response occur by this means, a decreased integrated reflex sensitivity would result. An altered central venous pressure/cardiac transmural pressure relationship, therefore, can be considered a plausible mechanism by which acute exposure to microgravity might lead to less baroreflex sensitivity than that seen during 6° head-down tilt.

If an altered central venous pressure/cardiac transmural pressure relationship is the only explanation for the significantly lower microgravity BRSIs measured in the present study the mean values measured by Schlegel and co-workers (1998) for subjects in the seated position during parabolic flight would be similar. The mean microgravity BRSI (20.6 ms.mmHg^{-1}) measured by these investigators, although less than the values measured in the supine and seated postures at +1G (25.8 and 24.7 ms.mmHg^{-1} respectively) were not significantly different. The use of the supine position during microgravity in the present study, however, may provide an initial cardiovascular state very different to that of the seated posture as a result of the high hydrostatic pressure gradient which would have been present during the 20 s of +1.8G immediately preceding microgravity.

Johns and colleagues (1994) report that entering parabolic flight induced microgravity from the supine position resulted in an increase in left-sided cardiac filling, a finding supported by Frey and associates (1990) and Buckey and co-workers (1996) with regards to orbital microgravity, whereas right-sided filling may be unchanged (Frey et al., 1990). Entering microgravity from the seated position, however, produced the reverse i.e. no change in left chamber filling but augmented right-sided filling (Johns et al., 1994). The authors suggest that the right heart and pulmonary vasculature may have been 'pre-filled' by the supine position, as opposed to the lower thoracic blood volumes that would have existed when seated upright. Consequently, little further change in right heart volume would occur on entry to microgravity when supine, however, microgravity induced alterations of thoracic pressures and thus fluid distribution, could lead to augmented left heart filling from the pulmonary vascular bed. It might be speculated therefore that a major difference between 6°head-down tilt and acute entry into microgravity could be the cardiac chamber filling profiles. In both cases increased filling of the right ventricle will have occurred by the time a Valsalva's manoeuvre is performed. Left chamber volume, however, will already have increased to some extent during head-down tilt by the time the Valsalva's manoeuvre is initiated, but on entry to microgravity an additional augmentation of left chamber filling occurs over and above that seen at +1G. This would lead to the performance of the Valsalva's manoeuvre during a greater state of left ventricular volume loading. Performing Valsalva's manoeuvres on entering microgravity, therefore, may raise the left heart baroreceptor group contribution to the integrated baroreflex response above that produced by 6°head-down tilt and thus a lower reflex gain than that noted during head-down tilt would

result. This mechanism would allow for similar cephalad shifts in body fluid for both conditions but a greater cardiopulmonary contribution to integrated reflex control in microgravity.

The subject position and the length of time in position prior to performing a Valsalva's manoeuvre may have an affect upon BRSI. Significant increases in stroke volume and cardiac output (Tomaselli et al., 1987) and decreases in heart rate (Tomaselli et al., 1987; Evetts and Russomano, 1995) have been measured after as little as 1 min at 6°head-down tilt. Nixon and co-workers (1979), however, report no changes in left ventricular diameter after 30 min at 5° head-down tilt. It appears that gravity induced changes in thoracic blood volumes and related cardiac indices occur within 1 to 4 min of head-down tilt, with a slower adaptation phase occurring thereafter leading to a reversal of the acute cardiac changes within 5 to 30 min, i.e. stroke volume and cardiac output ultimately drop below, and heart rate increases above, baseline levels (Tomaselli et al., 1987).

The subjects in the present study adopted the head-down tilt position 2 to 3 min before the first Valsalva's manoeuvre and remained in this position for approximately 10 to 15 min. Similarly, they remained supine for periods of about 15 min when performing Valsalva's manoeuvres in flight, however, microgravity was entered every 3 min thus continually disturbing any slow adaptation to the supine position. Consequently, although some Valsalva's manoeuvres were performed during acute physiological adaptation periods for both head-down tilt and microgravity, i.e. within 4 min, there is the possibility that some slow adaptation may have occurred towards the end of the head-down tilt period. This could result in slightly different physiological baseline conditions for the Valsalva's manoeuvres performed during the latter stage of head-down tilt. If this is the case then the magnitude of the acute changes in cardiac function e.g. increased stroke volume, may be diminished as slow adaptation acts to return these variables to baseline levels. This mechanism might therefore lead to only small changes in head-down tilt mean BRSI value when all responses to Valsalva's manoeuvre are statistically examined as a single sample. Clear trends in the BRSI values for this study, however, were not apparent. The identification of a trend is made difficult by the fact that head-down tilt measures were taken in groups of only three Valsalva's manoeuvres, and because the large natural variation associated with baroreflex responses could easily mask small differences resulting from slow physiological adaptation.

If this proposition is accepted, however, it would be advisable for subjects to return to a head-up position after each head-down tilt Valsalva's manoeuvre in order to prevent any chronic adaptation masking an acute affect on BRSI.

5.11 EFFECT OF DETRAINING UPON THE INTEGRATED BAROREFLEX RESPONSE.

The measurement of BRSI by means of Valsalva's manoeuvre in the present study was reliable as shown by the similar means for each parabolic flight and by the similarity between the mean BRSIs measured by Schlegel and colleagues (1998) and that of the current study and yet it was surprising that no significant effect of detraining upon BRSI was observed considering the differences in baroreceptor group gains and increased tolerance to LBNP associated with detraining.

In an investigation of the relationships between 8 methods of measuring baroreflex sensitivity, Goldstein and colleagues (1982) found that the average correlation between methods was 0.36 ($p < 0.01$) which although significant, indicated that a great deal of the variance between the measures was due to extraneous variables. Despite this low mean correlation the authors did find that carotid baroreflex gain[21] showed a highly significant correlation with BRSI measured from phase IV of the Valsalva's manoeuvre ($r = 0.7$, $df = 29$, $P < 0.01$). In this case considerably less variation was attributed to uncontrolled variables. Examination of the relationships between the baroreceptor sensitivities measured in the present study showed that carotid baroreflex gain was significantly related to the BRSI values measured during head-down tilt ($r = 0.92$, $df = 6$, $p < 0.01$), when seated ($r = 0.83$, $df = 6$, $p < 0.05$) and during microgravity ($r = 0.85$, $df = 6$, $p < 0.01$). The poorer relationships found by Goldstein and co-workers (1982) may be due to the use of a protocol which may not have successfully isolated carotid sinus function. For their measures the use of 10 s applications of neck suction was by their own accounts sufficiently long enough to have affected arterial pressure and thus derive contributions from aortic and cardiopulmonary baroreceptor groups. Furthermore their derivation of BRSI by means of phase IV of the Valsalva entailed the use of the entire post expiratory effort response which normally includes several systolic arterial pressure pulses which are not associated with lengthening R

[21] Measured by means of neck suction using an Eckberg collar

– R interval i.e. have not elicited a baroreflex response. Their BRSI values will therefore have been 'diluted' by data unrelated to the carotid baroreflex.

It would appear that the carotid sinus baroreflex gain is related to the reflex gain derived from phase IV of Valsalva's manoeuvre, however, no relationship was noted between cardiopulmonary baroreflex gain and the integrated BRSI for the present study. The derivation of BRSI by the use of R – R interval changes to systolic arterial pressure change is of course highly dependent on altered efferent activity to the cardiac pacemaker. The contribution from cardiopulmonary baroreceptors although present, primarily effects the diameter of peripheral vasculature (Abboud and Thames, 1983) and due to it's longer latency influences BRSI only marginally during the few seconds of phase IV of Valsalva's manoeuvre. The derivation of the cardiopulmonary baroreflex gain by means of LBNP and venous occlusion plethysmography in the absence of a change in mean arterial pressure indicates there is little arterial baroreceptor influence upon the reflex gain measured by this method. The lack of relationship between the two measures, therefore, is understandable.

If the BRSI derived from Valsalva's manoeuvre is considered to be primarily an arterial baroreflex with a secondary influence from the cardiopulmonary baroreceptors, the measure observed might be considered to be related to that of the combined response from aortic and carotid arterial receptor groups. On face value this seems reasonable, because the lack of change of BRSI with fitness could be explained by the decrease in carotid baroreflex gain and hypothesised increase in aortic baroreflex gain with detraining i.e. the alterations in individual arterial baroreflex gain could be mutually exclusive and result in no overall change in BRSI. The total arterial baroreflex response, however, was estimated to be slightly greater in the moderately fit (detrained) state than that of the highly fit state which would suggest that the detrained BRSI should be greater.

Although alterations in the gravity vector significantly changed the BRSI, mean values were not different between trained states for all conditions. The earlier calculations of carotid and aortic baroreflex gains were undertaken assuming a tonic inhibitory influence by the cardiopulmonary baroreceptor group in a resting state. If simultaneous stimulation of the arterial and cardiopulmonary baroreceptors occurs, as elicited with the Valsalva's manoeuvre, the degree of inhibition by the cardiopulmonary baroreceptors will vary according to trained state. During phase IV of the Valsalva's manoeuvre a significant increase in venous return occurs, resulting in stimulation of the cardiopulmonary

baroreceptors. If a negative relationship does indeed exist between aerobic fitness and this receptor group greater sensitivity of the cardiopulmonary baroreflex exists in the detrained state than the trained. Consequently a greater magnitude of central inhibition of the arterial baroreflex would occur during cardiopulmonary baroreceptor stimulation such as that produced by phase IV of the Valsalva's manoeuvre. It may be, therefore, that although the detrained state boasts a more sensitive arterial baroreflex in circumstances in which cardiac volume/pressure is unaltered, an increase in cardiac volume/pressure will produce a greater inhibition of this reflex by cardiopulmonary baroreceptors than would occur in the trained state thus producing an integrated response similar to that of the trained state for which a lesser degree of inhibition of a less sensitive arterial baroreflex occurs. This mechanism, therefore, offers an explanation as to how the BRSI, derived from the central integration of arterial and cardiopulmonary baroreceptor afferent activity, does not change with fitness despite the fact that the individual baroreflexes do.

5.12 LIMITATIONS

The variability of the baroreflex response and the methods and conditions employed to examine them e.g. Valsalva's manoeuvre, indirect arterial pressure measurement, venous occlusion plethysmography and in particular parabolic flight, are such that some experimental limitations were inherent in the methods and the design of this study. Although multiple measurements and strict experimental control were adopted throughout the possibility of that unrepresentative results could have been derived cannot be ruled out.

With regards to methodological limitations a mechanism by which BRSI results could be confounded is that of altered arterial pulse wave characteristics. No research as yet has been conducted to examine the effects of blood redistribution and changes in compartmental and tissue pressure (as occurs during microgravity) upon the propagation characteristics of the arterial pulse wave. If a general alteration in vascular compliance occurs on entry to microgravity a change in the magnitude of the digital pulse wave might result which, due to the use of Portapres to measure digital arterial pressure, could affect BRSI calculation. Certainly no definitive statement concerning the effects of acute exposure to microgravity upon integrated baroreflex gain derived from the response to Valsalva's

manoeuvre should be made until the use of non-invasive, digital arterial pressure measurement in microgravity has been examined in detail.

A second methodological limitation might be considered to be that the full sigmoid carotid baroreflex relationship was not measured in the present study. The principle element of the relationship to be studied, however, was that of gain which can be ascertained solely by the use of neck suction as a stimulus to the carotid sinus. For this reason, therefore, the neck cups used were not fabricated to apply pressure and full sigmoid relationships were not used for analysis.

Although the methods used to measure cardiopulmonary baroreflex gain have been employed by numerous researchers it must be recognized that invasive venous pressure measurement concomitant with LBNP and venous occlusion plethysmography does not offer the subject a condition in which relaxation is easy and thus involuntary muscular effort and thus efferent sympathetic activity cannot be ruled out.

A fourth methodological limitation was the choice of apparatus used for fitness assessment. The use of the cycle ergometer[22] during the measurement of $\dot{V}O_2max$ may have resulted in slightly lower values than would have been obtained using a treadmill. Although test-retest comparisons were of interest for this study and therefore absolute values were not required, comparison of these results with those of other studies using treadmills must be considered in the light of the possibility that absolute mean $\dot{V}O_2max$ values for the present study may be in the region of 5% low.

One principle design limitations was that plasma volume was unable to be measured during the parabolic flight aspects of the study. Loss of plasma volume has been proposed to be a factor that may complicate the interpretation of Valsalva's manoeuvre responses (Fritsch-Yelle et al., 1994). It is possible that subjects for this study may have restricted fluid intake in order to avoid the need to urinate during parabolic flight (no toilets on board), but the cabin environment was not overly hot and the time from aircraft door closure to door open was only 3.5 – 4 h. Any dehydration, therefore, would have only been mild. The possibility that fluid shifts during this study may not have followed those recorded in previous work cannot be discounted due to the lack of data concerning hydration state and central venous pressure. However, the nature of parabolic flights as opposed to the conditions inherent with

[22] Adopted for health and safety reasons.

space flight, are such that fewer extraneous variables will have been present that may have affected fluid volumes and so it is unlikely that hypovolaemia levels akin to those produced by space flight were present.

A second design limitation is that the nature of parabolic flight is such that not only is the physiology of the subject affected but also the emotional state. The experience of microgravity is such that a truly neutral, impassive state is unlikely. The interpretation of results, therefore, must be conducted with this in mind.

Finally, the nature of the experimentation and study designs required to examine aspects of human physiology associated with orthostatic tolerance and fitness is such that subject group size is invariably small. The confirmation of the results reported in previous work has therefore taken considerable time and is still not conclusive. Similarly the small sample size used in the present study is such that definitive statements concerning the findings cannot be made and that the nature of the relationships and function of the variables studied will only be known after subsequent research has been conducted.

5.12 CONCLUSIONS

Three questions were posed at the start of the study the answering of which, it was hoped, would confirm or refute the hypotheses stated.

- **Does exercise training lead to orthostatic intolerance?**
  - Endurance exercise training may lead to reduced orthostatic tolerance from elevated levels if undertaken to increase fitness beyond a moderately fit state (e.g. $\dot{V}O_2max$ greater than about 55 $ml.kg^{-1}min^{-1}$).

- **Do exercise trained individuals have altered baroreflex sensitivity during exposure to microgravity when they are fit compared to when they are unfit (detrained)?**
  - The state of endurance fitness does not appear to have an effect upon the integrated baroreflex response (as measured using Valsalva's manoeuvre) observed during acute exposure to microgravity.

- **Are the carotid and/or cardiopulmonary baroreceptors affected by training and if so, to what degree?**
  - Carotid baroreflex gain is increased by endurance training. High endurance fitness (64 $ml.kg^{-1}min^{-1}$) can lead to a 55% increase in gain from that of the moderately trained state (54 $ml.kg^{-1}min^{-1}$).
  - Cardiopulmonary baroreflex gain is significantly less (-25%) in the trained state (59 $ml.kg^{-1}min^{-1}$) than in the untrained state (45 $ml.kg^{-1}min^{-1}$), but does not significantly alter with a change in $\dot{V}O_2max$ when resting central venous pressure remains unchanged.

With regards to the hypotheses:

- **Trained endurance athletes exhibiting exercise-training induced hypervolaemia will show poorer orthostatic tolerance (as measured by progressive LBNP) than in the detrained, euvolaemic state.**
  - The principle hypothesis was supported, however, detraining appeared to improve tolerance to a level greater than that of the trained state.

- **Trained endurance athletes exhibiting exercise-training induced hypervolaemia will show more sensitive integrated baroreceptor function (more pronounced slowing of the heart for given arterial pressure increases) both at +1Gz and during microgravity when in an unfit (exercise detrained) state than when in a fit (trained) state.**
  - The second hypothesis was not substantiated due to a lack of change in integrated baroreflex gain with detraining.

- **Cardiopulmonary baroreceptor sensitivity will increase (greater peripheral vascular constriction for a given fall in central venous pressure) as a result of a reduction of endurance fitness sufficient to lower exercise-training induced hypervolaemia to euvolaemic levels.**
  - This hypothesis was partially substantiated in that the test group mean gain (trained and detrained states combined) was significantly less than the control mean gain. No significant change, however, was measured as a result of detraining in the test group.

- **Carotid baroreceptor function will show no change as a result of a reduction of endurance fitness sufficient to lower exercise-training induced hypervolaemia to euvolaemic levels.**
  - The final hypothesis was not substantiated due to the significant decrease in carotid baroreflex gain in the detrained state.

The notion that endurance exercise training may impair tolerance to orthostatic stress originated from a number of studies at about the time of the space Apollo missions and initiated debate concerning whether a true cause and effect existed and whether there might be an optimal endurance fitness for astronauts. Research in the intervening decades has not resolved the debate. The two principle reasons for this may be the choice of subjects and differences in the methods employed to measure orthostatic tolerance. A significant hindrance to the resolution of the question has been the choice of stressor. The two principle methods used i.e. head-up tilt/stand tests and LBNP not only differ in the magnitude of stress imposed upon the subject, but also in the form of stimulus applied to the carotid baroreceptors. The relative contributions of acute reflex and chronic neuroendocrine systems

to the maintenance of arterial pressure during orthostasis is therefore potentially different for each method, with the result that physiological states and tolerance may differ.

Investigators appear to be divided into three schools of thought, those who believe a positive relationship exists between endurance fitness and orthostatic tolerance, those believing a negative relationship exists and those who do not believe a relationship exists. The hypothesized 'parabolic relationship' proposed by Ben Levine in 1993 offers a model in which all three views can hold. This model shows how improved tolerance can be observed with endurance training when fitness is increased from low to moderate levels. Continued exercise training may then decrease orthostatic tolerance thus showing a negative relationship for this section of the model. Additionally a lack of relationship may be observed if the orthostatic tolerance of subjects of very high and very low fitness are compared. It is highly likely, therefore, that the choice of cross sectional comparisons of subject groups with different levels of aerobic fitness, or longitudinal investigations of the effects of increasing aerobic fitness from a low level to moderate level or from moderate to high level or examinations of the effects of detraining, can all produce results which appear contradictory if a simple linear relationship is believed to exist. The consideration of the results of all studies employing appropriate methods and definitions of orthostatic tolerance in addition to the results of the present study, however, indicates that Levine's parabolic model might resolve the debate.

A clearer picture of the issue is achieved when research data involving only one method are considered rather than by attempting to address the issue by examining all studies. The choice of LBNP as the principal method of examining orthostatic tolerance by NASA in the past has meant that more data exists in which this method has been employed than any other. Consequently by consideration of LBNP based studies alone the relationship between endurance fitness and tolerance to orthostatic stress becomes more evident.

A major adaptation to endurance exercise training is the augmentation of parasympathetic efferent activity and consequent attenuation of sympathetic efferent activity. This state provides the athlete with a physiological basis appropriate for long duration, high intensity exercise i.e. a low resting heart rate to increase the maximum heart rate differential available for cardiac output elevation and low vascular resistance to allow adequate perfusion of

exercising skeletal muscle during exercise. The results of the present study show that the highly fit state provides a tolerance to orthostasis which is less than that of the moderately fit state but equal to that of the untrained state. An endurance training induced reduction in aortic compliance with subsequent alteration in the visco-elastic coupling mechanisms of the baroreceptors, in combination with the heightened vagal efferent activity may cause a reduction of arterial baroreflex sensitivity (carotid + aortic) in the region of 65% less than that of the untrained state and 35% less than that of the moderately trained state. The reduced arterial baroreflex gain in the highly fit state occurs despite an increase in sensitivity of the carotid baroreflex derived from the augmented parasympathetic baseline, because of the decrease in the predominant aortic baroreflex. Increased myocardial compliance similar to that observed in the aorta may act to reduce cardiopulmonary baroreflex gain. Therefore heart rate does not increase and vascular resistance is unable to be maintained as effectively as seen in the less fit states. Furthermore, central inhibition of efferent sympathetic activity also appears to attenuate neuroendocrine secretion at rest and during hypotensive stress. The reduction in endocrine function, that is attenuated plasma renin activity and arginine vasopressin concentrations, during orthostasis leads to a reduced ability to defend blood volume and vascular resistance. Although these physiological adaptations to the highly trained state appear to indicate an attenuated ability to withstand orthostatic tolerance, significant training induced increases in blood volume, stroke volume, central venous pressure and cardiac output appear to offset the disadvantages to enable the highly trained athlete to have a similar level of tolerance to orthostatic stress as untrained subjects.

The finding of the present study that the detrained state provides an augmented tolerance to orthostatic stress may be due to a reversal of some but not all of the physiological adaptations previously attained in the highly fit state. Blood volume and stroke volume return to sedentary levels and resting heart rate increases. The heightened parasympathetic baseline associated with endurance fitness decreases thus reducing the braking effect upon sympathetic efferent activity, allowing the detrained athlete to more effectively increase heart rate, plasma renin activity, plasma arginine vasopressin concentrations and vascular resistance during orthostasis. Although these advantages provide the moderately fit athlete with a greater tolerance to orthostasis than the highly fit athlete, the retention of high

myocardial and aortic compliance with decreased blood volume may be responsible for a transient reductions in cardiopulmonary and aortic baroreflex gain to levels below those of the highly trained state. Consequently a decrease in cardiopulmonary baroreflex gain may occur temporarily until sedentary compliance is regained. Aortic gain, however, may increase despite reduced aortic compliance due to the decrease in cardiopulmonary baroreflex inhibition of efferent sympathetic outflow. A higher aortic gain is sufficient to offset the detraining induced reduction in carotid baroreflex gain thus providing a greater arterial baroreflex gain overall than seen in the highly trained state.

If the principle elements associated with orthostatic tolerance are effective increases in heart rate, increased plasma vasoactive hormone levels and the maintenance of vascular resistance, then in the absence of a more effective tachycardia during orthostasis than the untrained state (which is probably associated with the lower baroreflex gains) the moderately fit state may provide a more efficient neuroendocrine response to defend arterial pressure.

One of the principle mechanisms used to explain the differences in tolerance to orthostatic stress is altered baroreflex state with endurance fitness. A major finding of the present study, however, was that the integrated baroreflex does not change with fitness. This apparent disparity may be explained by the nature of the methods used to examine the relevant reflexes. It is increasingly apparent that the human cardiopulmonary baroreflex has an inhibitory effect upon that of the arterial. During increased stimulation of the cardiopulmonary receptors the inhibitory influence is increased thus reducing the efferent sympathetic activity derived from the arterial baroreflex. If the cardiopulmonary baroreflex gain is indeed greater in the less fit state than the high fit, a greater inhibition of arterial baroreflex function results with detraining. Although the arterial baroreflex gain may be higher in the detrained state during tonic inhibition by the cardiopulmonary baroreflex, the combination of high arterial baroreflex gain and high cardiopulmonary baroreflex inhibition (as with phase IV of Valsalva's manoeuvre) may produce an efferent response equal to that of the low arterial baroreflex gain and low cardiopulmonary baroreflex inhibition found in the highly trained state. Consequently, similar integrated baroreflex sensitivity may be observed. This effect is probably not evident or as acute during orthostasis because for all states of fitness reduced cardiac filling/pressure decreases cardiopulmonary baroreceptor

afferent activity thus reducing or possibly eliminating the inhibitory effect upon arterial baroreflex function therefore enabling contributions to occur from these receptor groups according to trained state.

An inhibitory influence of the cardiopulmonary baroreflex upon arterial baroreflex gain may also be the basis of the significantly lower integrated baroreflex gains measured during microgravity. An augmented inhibition may result from altered central venous pressure/cardiac and peripheral vascular transmural pressure relationships during microgravity. Additionally if the supine posture is adopted prior to entry to microgravity a rise in left-sided cardiac volume resultant from pressure equilibration on exposure to microgravity increases left ventricular cardiopulmonary stimulation and thus afferent activity. These mechanisms may sufficiently increase myocardial stretch and therefore cardiopulmonary stimulation to augment the cardiopulmonary contribution to the integrated response beyond that derived at 1G leading to a lower integrated baroreflex gain during microgravity.

5.13 IMPLICATIONS

The principle effect of endurance training associated with reduced orthostatic tolerance (compared to the moderately fit state) appears to be an alteration in baseline autonomic state (increased parasympathetic, decreased sympathetic efferent activity) which may be responsible for altering baroreflex gain and the neuroendocrine response to orthostasis. The findings of Fritsch-Yelle and colleagues (1996) in which significantly lower efferent sympathetic activity at rest and during post mission orthostatic stress was observed in astronauts, appears to show a similar physiological state to that of the highly trained athlete, but for moderately trained astronauts. The indications are that some individuals may posses an inherent pre-disposition towards such an autonomic state and that exposure to the microgravity environment and/or the conditions inherent with space missions may impose a physiological state upon the astronaut similar in some respects to that of a highly trained endurance athlete. The implication is that although astronauts are moderately fit, the enhanced tolerance to orthostatic stress offered by this state may be reduced by space travel and that should a highly fit astronaut be exposed to the microgravity environment, despite the possibility that their orthostatic tolerance may be 'normal', he/she might suffer a loss of tolerance to orthostasis on a return to earth as a result of exposure to microgravity which exceeds that of his/her moderately fit colleagues.

This potentially dangerous scenario could be exacerbated by the effect of endurance training upon the arterial baroreflex. Although high levels of endurance fitness appear to increase carotid baroreflex gain, it may be that arterial baroreflex gain overall (carotid + aortic) is reduced. As the work of the team headed by Eckberg and Fritsch clearly show reductions in carotid baroreflex gain during the course of short duration space missions, the possibility exists that an inadequate (for orthostasis) arterial baroreflex capability in highly fit astronauts could be worsened by chronic exposure to microgravity consequent to a further loss of orthostatic tolerance on a return to earth.

Other implications of the results of this study are firstly, does the possibility exist that astronauts undertaking regular exercise training to maintain fitness during long duration space missions may adversely affect their tolerance to orthostasis should they increase their

endurance fitness too much? Secondly, if an astronaut increases endurance fitness to a very high level prior to a short or medium term mission, could he/she allow endurance fitness to decrease during the mission (whilst concentrating on maintaining strength) with a resulting improvement of orthostatic tolerance similar to that observed in the present study which might offset the detriment caused by the exposure to microgravity? That is, could a loss of endurance fitness from a high level to moderate level during space missions be used as a counter measure to microgravity induced orthostatic intolerance?

Orthostatic intolerance can be considered to occur when a significant 'postural' induced decrease in central blood volume and cardiac filling pressure results in inadequate perfusion pressure to the essential organs. Although the highly trained state may appear to be inappropriate for this challenge, in most cases training induced adaptations such as hypervolaemia and a greatly increased stroke volume and cardiac output sufficiently offset the disadvantages mentioned, to enable 'tolerance' to be maintained at 'normal' levels i.e. similar to that of the untrained. Consequently, the suggestion often made that the highly trained endurance athlete may show poor orthostatic tolerance may be inaccurate and it might be more appropriate to say that the moderately trained endurance athlete shows improved tolerance. The interesting question remains, however, as to whether the untrained individual who becomes moderately trained improves tolerance to a level equivalent to that of the individual who detrains to become moderately fit. The overall implication of this study is that both the highly trained endurance athlete and the untrained sedentary individual may be more intolerant to orthostasis after space travel than their moderately endurance trained counterpart, which coincidently and fortunately is the average level of fitness for present day astronauts.

APPENDICES

September 1995

RESEARCH ETHICS COMMITTEE PROPOSAL

INVESTIGATORS MUST REFER TO THE NOTES OF GUIDANCE BEFORE COMPLETING THIS FORM

Confidential - not for publication

KING'S COLLEGE LONDON

APPLICATION FOR APPROVAL OF A RESEARCH PROJECT INVOLVING HUMAN SUBJECTS

(Please complete all sections; investigators should note that the Committee will not accept incomplete applications.)

1) BRIEF TITLE OF PROJECT

THE EFFECT OF REAL AND SIMULATED MICROGRAVITY AND PHYSICAL FITNESS ON BARORECEPTOR FUNCTION

2) TYPE OF INVESTIGATION (FOR DATA COLLECTION PURPOSES)

Complete and delete as appropriate

a) Is the Study based solely on questionnaires, or other research not involving invasive techniques? ~~Yes~~/No

b) Does the Study involve invasive techniques? Yes/~~No~~

c) Does the Study involve the use of drugs? Yes/~~No~~
If the answer is YES, please state which phase the Study falls into: Phase1/Phase2/Phase3/Phase4

d) Are any of the investigators students of King's College, London? Yes/~~No~~

Please estimate numbers of volunteers participating in the Trial:

Patients (Over 18 years) Number:.....0.....

Healthy volunteers (over 18 years) Number:.....20.....

Patients (under 18 years) Number:.....0.....

Healthy volunteers (under 18 years) Number:.....0.....

f) Is the Study being conducted in association with a sponsor e.g. a manufacturer-organised drug trial: ~~Yes~~/No

3) APPLICANT(S) (One must hold a contract of employment with King's College London)

Principal Investigator (Normally a member of the Academic Staff to whom correspondence should be addressed. The principal investigator of a student project must be the supervisor.

NAME: John Ernsting ..... POST ..Professor.... DEPT ...Physiology

Qualifications	Previous experience of Research on Human Subjects
MB BS, PhD, FRCP	25 years of human cardiorespiratory research

Other Investigators	Host Institution	Employed by	Qualifications	Previous Experience of Research
Simon Evetts	KCL		BA(Hons)	2 years fitness assess experience
			MSc	1.year.Human.Physiology research

Head of Department

Professor P McNaughton

Head of Section

Professor J Ernsting

Medical Supervisor (see notes - must be UK registered and insured).

Name	Qualifications	Post
J Ernsting	MB BS, PhD, FRCP	Visiting Professor

Location of Medical Supervisor during this research: ...will be present throughout as one of the investigators

REC Protocol Number .../.....

Signatures of Applicants

Principal Investigator ..... J Ernsting .....

Date ...2 Sept 1996.....

Medical Supervisor ..... J Ernsting .....

Date ...2 Sept 1996.....

Head of Department ..... J Ernsting pp P McNaughton .....

Date ...2 Sept 1996.....

Communications about this application should be addressed to:

Name: ..Professor J Ernsting / Mr Simon Evetts.....

Address: (full postal address please) ..Physiology Group, Biomedical Sciences Division,.....

King's College London, Campden Hill Road

.....

LONDON W8 7AH U. K.

.....

Telephone No: ..0171 - 333 4175 / 4176.....

Fax No: ..0171 - 333 4008.....

Name of any other administrators who may be contacted:

Name: .....

Telephone No: .....

Fax No: .....

REC Protocol Number .../.....

4) Preferred Timetable

Nature of project: U/G BSc, P/G MSc, (P/G PhD), Other .....

Preferred start date: 2 October 1996

Date of submission of project: Summer 1999

5) SPONSOR

Please name organisation on whose behalf the work is undertaken

Kings College London Yes/~~No~~ (If no please specify) .....

Funding Organisation ..KCL; applications to be made to MRC and other potential sponsors

6) PURPOSE OF STUDY (Describe the rationale for the study within the context of present knowledge and state the anticipated benefits. Explain the specific objectives of the study and where appropriate the hypotheses to be tested. For each hypothesis state the end-points to be used.)

Please see attached sheets

AN INVESTIGATION INTO THE EFFECTS OF MICROGRAVITY, SIMULATED MICROGRAVITY AND TRAINED STATE ON BARORECEPTOR FUNCTION.

PROPOSAL FOR A RESEARCH STUDY UNDERTAKEN BY S N EVETTS AT KING'S COLLEGE, LONDON

There is evidence to suggest that endurance-trained athletes fail to maintain adequate blood pressure responses when exposed to gravitational challenges such as standing and head-up tilt (6, 9, 15, 22, 24). Observations from both space missions and ground based simulations of microgravity indicate that astronauts also Have less tolerance to gravitational stress post mission, i.e. they have a lower orthostatic tolerance (7, 13, 24, 25).

Investigations of blood pressure control mechanisms have derived results indicating differences in baroreceptor sensitivity between athletes and non-athletes and between the pre and post-mission states of astronauts (1, 7, 15, 25). Alterations in baroreceptor function of the two groups of receptors, i.e. high pressure (aortic and carotid) and low pressure (cardiopulmonary), have been implicated as sources of the overall differences in sensitivity (3, 5, 7).

Certain other factors may have a direct or indirect bearing on orthostatic tolerance post training and/or microgravity exposure, examples of which are the mode and degree of training, body build, blood volume, vascular distensibility and genetic predisposition (3, 9, 14, 25). Although many previous studies have examined one or more aspects of this area of interest (11, 14, 19, 24), it is only now that the mechanisms are becoming sufficiently understood that properly controlled investigation of the pertinent elements of the control system is possible. Body build for instance may affect the issue through the effects of leg muscle mass on vascular compliance (14).

The results of previous work have not resolved the question of whether fitness per se or an inherent predisposition to be able to become very fit leads to orthostatic intolerance. Additionally, a definitive statement concerning the length or degree of training that might be necessary to induce this condition has not been made. Observations do, however, suggest that training induced hypervolaemia may play an important role in the derivation of orthostatic intolerance (3, 9, 22). It has been suggested that the length of training necessary to produce an effect on orthostatic tolerance is in excess of 6 months (3, 9, 14, 19). From literature reviews and preliminary work carried out at King's College, there are indications that it is highly endurance trained individuals who have developed recognised training induced hypervolaemia who are at risk of adversely altered baroreflex function. These individuals if presented with a second condition detrimental to blood pressure control, such as microgravity, could be open to a cumulative adverse effect on orthostatic tolerance. So far astronauts have been found to possess average fitness levels, however, disaster might occur if a very fit STS pilot or commander had to react to an unforeseen event during shuttle re-entry ?

The purposes of this study are to ascertain whether training or genetic endowment predispose humans to low orthostatic tolerance and to examine which elements of the baroreflex system are affected by microgravity exposure, and to what degree, for subjects in a trained and untrained state.

SPECIFIC AIMS:

1. To ascertain the effects of 6 hours of simulated microgravity upon the functioning of high and low pressure cardiovascular baroreceptor groups.

2. To ascertain the effect a highly exercise trained state has upon the function of high and low pressure baroreceptor groups.

3. To examine whether trained state or genetic endowment predisposes an individual to differences in baroreflex function.

4. To investigate whether a difference in baroreflex sensitivity is associated with an acute exposure to microgravity and, should an effect be found, whether this change is the same for trained and untrained states.

HYPOTHESES:

1. Both carotid and cardiopulmonary baroreceptor function will be affected by 6 hours of simulated microgravity.

2. Highly trained endurance athletes will have a less responsive baroreflex before and after 6 hours of microgravity simulation when compared to the detrained state.

3. Altered baroreflex function is as a result of endurance training rather than a genetic predisposition.

4. There is a difference in the baroreflex responses to acute exposure to microgravity between trained and detrained states.

7) STUDY DESIGN AND METHODOLOGY

Outline of the Proposed Project - Describe and justify the project's overall design, the procedures to be used, measurements to be made, the frequency of visits to the Hospital, College or other location and the duration of the project.

Please see attached sheets

DESIGN AND METHODOLOGY

The study will follow a repeated measures design to enable changes in baroreceptor responses to be measured before and after 3 conditions; exposure to microgravity, exposure to simulated microgravity (head down tilt) and detraining.

Eight male or female athletes and eight non-athletic control subjects aged between 18 and 45 years will be recruited from King's College London, the local student community and the local athletic community by means of poster displays and letters to club coaches. Volunteers with a history of cardiovascular, respiratory and/or CNS disease or evidence of any other disease during clinical examination will be excluded. The examination will include a resting 12 lead ECG. Subjects will be required to provide informed consent.

The study is essentially divided in to 7 phases:

PHASE 1: TECHNIQUE DEVELOPMENT AND VALIDATION. The initial stage of the study will involve the development and validation of the procedures and apparatus to be used. Healthy subjects will be recruited from amongst hospital/college staff and students for these trials.

PHASE 2: SUBJECT RECRUITMENT AND REHEARSAL PERIOD. Subjects will be actively recruited during phase 1 but the medical examination and final selection will not be undertaken until phase 2. All successfull candidates will have their maximum oxygen uptake levels (VO2max) measured and a check to ensure that they can micturate when at 6 degrees head-down tilt (HDT) will be made. Each subject will undertake a training morning for test familiarisation and will be trained in the procedures that they will be subjected to. They will be allowed to practice these until familiarity is achieved.

PHASE 3: FIRST PARABOLIC FLIGHT. Once the subject has successfully passed all assessment criteria he/she will enter the first stage of experimentation. This stage will involve cardiovascular measurements at rest, namely:

1. Blood Volume by the Evans blue dye dilution method.
2. Baroreflex sensitivity index (BRSI) determined by measuring heart rate and arterial pressure responses to Valsalva's manoeuvres or carotid sinus stimulation using a neck suction/pressure cuff.

These measurements will be followed by short exposures (20 to 30 seconds) of microgravity whilst on board European Space Agency Airbus A300 flights. During these parabolic flights baroreflex sensitivity will be measured at least 5 times during 5 different exposures to microgravity. Post flight BRSI measurements will also be made.

PHASE 4: FIRST BARORECEPTOR FUNCTION ASSESSMENT AND HDT PERIOD. After baroreceptor function has been measured the high and low pressure components of the baroreflex system will be examined at +1Gz. High pressure (carotid) baroreceptor function will be assessed using the neck suction/pressure cuff. Low pressure (cardiopulmonary) group function will be assessed using a lower body negative pressure (LBNP) box. Both assessments will be carried out in the horizontal position whilst the subject is at rest. Closed loop baroreceptor sensitivity will be assessed by means of Valsalva's manoeuvres.

After these assessments the subject will undergo 6 hours of 6 degree head down tilt to simulate microgravity conditions. For 2 minutes during every 15 minute period, blood pressure and heart rate will be measured.

Immediately after the 6 hours of head down tilt the subject will undergo high and low pressure baroreceptor group function assessment once again. These assessments will be carried out before the subject is allowed to sit or stand.

PHASE 5: DETRAINING PERIOD. The test group (athletes) will cease from all physical training for a period of 6 months. During this period the subjects will have monthly VO2max and blood volume measurements. Once the test groups' blood volumes have been within a normal range for blood volume for at least one month or after 6 months of detraining (which ever occurs first) phase 5 will end. Control subjects will maintain their normal daily activity level during this period. Final blood volume and VO2max measurements will be carried out within 48 hours of the start of phase 6.

PHASE 6: SECOND BARORECEPTOR FUNCTION ASSESSMENT AND HDT PERIOD. A repeat of phase 4 will assess the functioning of high and low pressure baroreceptor groups before and after 6 hours of microgravity exposure in the detrained subjects and controls. All procedures will be identical to those used in phase 4.

PHASE 7: SECOND PARABOLIC FLIGHT. Subjects will undergo the same cardiovascular measurements as performed in phase 3. Similarly, each will experience a second series of exposures to microgravity during a parabolic flight to assess baroreflex function.

SUMMARY OF STUDY PROTOCOL

PHASE 1.	TECHNIQUE DEVELOPMENT & VALIDATION. RECRUITMENT OF SUBJECTS.
PHASE 2.	RECRUITMENT OF SUBJECTS. MEDICALS AND FITNESS TESTS. REHEARSAL AND PRACTISE PERIOD FOR SUBJECTS.

PHASE 3. BLOOD VOLUME & BRSI ASSESSMENT AT REST.
PARABOLIC FLIGHT - BRSI ASSESSMENT IN MICROGRAVITY.

PHASE 4. LBNP AND NECK CHAMBER MEASUREMENTS PRE 6 HRS HEAD DOWN TILT.
6 HRS OF 6 DEGREE HEAD DOWN TILT.
LBNP AND NECK CHAMBER MEASUREMENTS POST 6 HRS HEAD DOWN TILT.

PHASE 5. DETRAINING PERIOD (6 MONTHS).
BLOOD VOLUME AND MAXIMAL OXYGEN UPTAKE MEASURED MONTHLY.

PHASE 6. LBNP AND NECK CHAMBER MEASUREMENTS PRE 6 HRS HEAD DOWN TILT.
6 HRS OF 6 DEGREE HEAD DOWN TILT.
LBNP AND NECK CHAMBER MEASUREMENTS POST 6 HRS HEAD DOWN TILT.

PHASE 7. BLOOD VOLUME & BRSI ASSESSMENT AT REST.
PARABOLIC FLIGHT - BRSI ASSESSMENT IN MICROGRAVITY.

SPECIFIC EXPERIMENTAL PROCEDURES

1. Maximal Oxygen Uptake Test. Aerobic fitness will be measured through the use of a maximal exercise test (20). The subject, having been screened for any health risk factors and following a warm up, will be asked to run on a treadmill at progressively increasing intensity. He/she will exercise at each intensity for two minutes during which mixing box collection of expired air will be made. Oxygen uptake will be measured at each stage using oxygen and carbon dioxide analysers and gas volume meters. The subject will be asked to continue progressing through the increasing intensities until he/she feels unable to continue, i.e. volitional exhaustion. Heart rate will be monitored and recorded by means of a three lead ECG and relative perceived exertion (RPE) recorded at 2 minute intervals. The criteria for an early cessation of the test are as given in the 'Hazards' section.

The ECG will be recorded for three minutes following cessation of exercise. The subject will remain near and report to the medical staff for a period of 15 minutes after completion of the test.

2. Blood Volume. The Evans blue dye technique involves the injection of T-1824, a harmless dye (17), in to an antecubital vein of the resting, supine subject. A sterile venous catheter will be introduced into a vein of the hand or antecubital fossa from which 5 ml venous blood samples will be drawn. The blood samples will be taken 10, 20, 30, 60, 90 and 120 minutes after the injection of the dye. Plasma volume will then be calculated by the dye dilution method (17).

3. Valsalva Manoeuvre. Barcreflex sensitivity index will be calculated from heart rate and blocd pressure measurements taken during Valsalva's manoeuvre. This manoeuvre has been successfully employed as a test cf circulatory and autonomic function for a number of years (12). The subject will be required to maintain an expiratory pressure of 40 mmHg against a closed tap for a period of 15 seconds. Between 5 and 7 Valsalva's manoeuvres will be performed until at least 3 consistant heart rate/blood pressure responses have been recorded. Arterial pressure will be recorded by means of a Ohmeda 2300 Finapres and heart rate by an ECG. Should the subject feel any chest, neck or head pain, feel unduly dizzy, be unable to maintain the expiration or show indications of pre-syncope the manoeuvre will be discontinued.

4. Lower Body Negative Pressure. The cardiopulmonary baroreceptor reflex sensitivity will be measured by applying suction to the lower body by means of a lower body negative pressure (LBNP) box, and recording central venous pressure (CVP), forearm blood flow, heart rate and arterial pressure (11,15). Negative pressure of up to -20 mmHg will be exerted upon the lower body for 3 minutes during which forearm blocd flow and CVP will be measured continuously. Prior to this 3 minute period the subject will undergo a 20 minute resting period during which baseline heart rate, blood pressure, CVP and forearm blood flow measurements will be taken. Every 20 seconds during the 3 minute test period forearm blood flow will be determined using venous occlusion plethysmography, arterial pressure will be recorded non-invasively using the Finapres finger arterial pressure method (18) and CVP will be recorded using the Gauer and Sieker (1956) dependent arm technique. Cardiopulmonary barcreceptor sensitivity will be calculated from the ratio of change in CVP divided by change in forearm vascular resistance as derived from the venous occlusion plethysmography measurements (26). The 3 minute LBNP test period may be repeated up to 3 times. A 5 minute recovery period following the LBNP period will ensure subject recovery is adequate before leaving the horizontal position.

5. Venous Occlusion Plethysmography. Forearm blood flow and thus vascular resistance will be measured using a mercury-in-silastic strain guage placed around the left forearm. A blood pressure cuff proximal to the elbow will be inflated to 30 - 50 mmHg to occlude venous return from the forearm. The circulation to the hand will be occluded by a cuff around the wrist inflated to 200 mmHg for the period of blood flow measurement. Measurements will be made for 10 second periods. Mean arterial pressure divided by blood flow will give forearm vascular resistance (26).

6. Central venous pressure. CVP will be monitored by the Gauer and Sieker (1956) method during LBNP. A catheter will be placed in an antecubital vein of the dependent arm. The subject will lie on his/her back or in the right lateral decubitus position throughout the experiment, with the right arm dependent in order that changes in peripheral venous pressure will reflect changes in CVP. The catheter will remain in position during the 20 minute baseline period, the 3 minute test period, the 5 minute recovery period and during head-down tilt, and the following 7 hours.

7. Neck Chamber Suction Technique. A tightly sealing rigid chamber with a rubber seal will be placed around the anterior aspect of the subject's neck. The chamber is connected to a motor driven pressure system capable of delivering sequential pressure changes to the chamber. A sequence of pressure and suction steps between -65 mmHg amd +40 mmHg will be delivered to the chamber during held expiration over a period of 7 seconds. Pressure/suction steps will be applied automatically, triggered by successive ECG 'R' waves (23). Responses measured using a 3 lead ECG for 5 successful repetitions of the sequence will be averaged. Arterial baroreceptor sensitivity will be expressed by the relationship between R-R interval and applied carotid distending pressure.

8. Head Down Tilt. Each subject will undergo the following protocol for microgravity simulation.

i. Rest in horizontal position for 20 minutes.
ii. Placed in a 6 degree head down position for 6 hours.
iii. Returned to horizontal position prior to second set of LBNP and neck chamber measurements.

The following variables will be recorded during the first and last 3 minutes of the 20 minute baseline period and during the last 2 minutes of every 15 minute period over the course of the 6 hours head down tilt.

i. ECG
ii. Digital arterial pressure by means of Finapres.
iii. Brachial arterial presssure by sphygmomanometer and auscultation.

During the head down tilt period the subject will not eat but will drink 200ml of water every 2 hours. He or she will be allowed to urinate in to a collection flask if necessary but will remain in the head down tilt position.

9. Microgravity. The ESA parabolic flights normally produce about 30 periods of microgravity lasting approximately 20-30 seconds. In between these periods are periods of eugravity and macrogravity up to about +3Gz. Subjects may feel some nausia after a number of microgravity exposures.

8) RISKS AND HAZARDS

Please describe the potential hazards and risks, specify the probability and seriousness of the hazard/risk.

Please see attached sheets

Please name the locations or sites where the work will be done (room number, etc.)

Rooms EG6 & 7; KCL, Kensington Campus

Please describe the facilities available and procedures planned to deal with any adverse reactions or untoward incidents.

Resuscitation kit including equipment for administering 100% oxygen

Please name the individual who will manage any adverse reactions:

Professor J Ernsting

9) SUBJECTS TO BE STUDIED

	MALE	FEMALE
Number of patients to be studied:	0	0
Upper age limit:		
Lower age limit:		
Number of healthy volunteers to be studied:	Total 20 either sex	
Upper age limit:	45	
Lower age limit:	18	

Please indicate how patients and/or volunteers are to be identified and recruited. Specify inclusion and exclusion criteria.

To be recruited by poster (copy attached) and poster/letter to Sports Clubs
Inclusion: healthy athletes with $\dot{V}O_2$ max $\geqslant$ 60 ml/kg/min
Exclusion: cardiorespiratory disease

Will travelling expenses be given (if so, an appropriate comment should be included on the Information Sheet)?

Yes

Is any financial or other reward, apart from travelling expenses, to be given to participants? If yes, please give details and justification.

Yes. £3 per hour and free meals. Cash up to a maximum of £90

SAFETY AND HAZARDS

1. General. Medical cover will be provided by Professor John Ernsting at KCL (Kensington). During any stress tests emergency CPR equipment will also be at hand, with which Mr S Evetts has had experience (Advanced Resuscitation Aug 1994 - Durham County Ambulance Service).

2. Maximal Oxygen Uptake Test. The hazards involved in the maximal stress tests are minimal, but are principally concerned with stressing the cardiopulmonary systems to a high intensity. Fatigue during maximal exercise involving large muscle masses primarily results from a inadequate cardiac output and tissue perfusion (21). The risks associated with such testing are minimal for healthy subjects under the age of 40 (20). The likelihood of severe complications such as myocardial infarctions or death resulting have been shown to be 0.000008% in a survey of 500,000 controlled maximal exercise tests carried out on healthy subjects and patients (5). The risks will be especially low with the athletes because they will almost certainly exercise to near maximal levels on a weekly basis. The ECG will be monitored continuously during the test.

MAXIMAL OXYGEN UPTAKE TEST CESSATION CRITERIA

a. Should the subject wish to discontinue the test for any reason.

b. Should any major ECG abnormalities such as continued marked depression or elevation of ST segments, be detected.

c. Should the subject indicate, or be seen to be experiencing:
- chest pains
- difficulty in breathing
- dizziness, light-headedness or lack of coordination.

d. Should the subject show signs of poor perfusion such as cyanosis or pallor.

e. Should the subject appear to be unduly distressed in any way other than through fatigue.

2. Valsalva's Manoeuvre. The risks associated with performing a Valsalva's manoeuvre are essentially concerned with the brief states of hyper and hypctension produced. As the subject exhales to 40 mmHg this pressure is transferred to the arterial system causing an increase in arterial pressure. A reduction in arterial pressure occurs shortly after when the increased intrathoracic pressure reduces venous return to the heart. Hypertension also occurs after expiration has ceased due to the sudden increase in venous return combining with the elevated cardiac output and peripheral vasoconstriction seen

during the manoeuvre. These are reflexly reduced within a few seconds post manoeuvre. In each case the blood pressure alteration is transient, of a short duration, and (using an expiratory pressure of 40 mmHg) not of sufficient magnitude to cause harm to healthy subjects (12).

3. Head Down Tilt. Bed rest with 6 head-down tilt has been used extensively over the last 15 years to simulate the effects of microgravity (4,13). Subjects have been placed in this position for continuous periods between 2 hours and 42 days. Adopting 6 hours of 6 degree HDT in a pilot study conducted at KCL produced no adverse effects in 8 subjects (19). Assumption of such a head-down position produces vascular congestion of the head and neck which gives rise to a feeling of fullness in the head and 'stuffiness' in the nasal passages.

4. Blood Volume Measurement. The hazards involved with the placement of a catheter in an anticubital vein are minimal. The possibility of a small amount of venous bleeding is present. The Evans blue dye (T-1824 Azovan Blue) used for blood volume measurement shows no side-effects other than slight temporary discolouration of the skin in some subjects (16). 5 ml of 1% dye solution will be injected and 5 x 5 ml blood samples will be taken over a period of two hours for each measurement. A total of 8 blood volume measurements for each subject will be made over the course of the study.

5. Central Venous Pressure Estimation. This procedure will utilise the catheter placed in the arm for blood volume measurement. Other than the hazards associated with this the procedure is harmless.

6. Venous Occlusion Plethysmography. No invasive techniques are employed. No discomfort or hazards are present other than the tightness of the cuffs around the wrist and upper arm.

7. Lower Body Negative Pressure. LBNP places some stress on the cardiovascular system as blood is displaced from the upper body to the vessels of the lower body. Prolonged exposure to LBNP values in excess of 30 mmHg can give rise to pre-syncope and vaso-vagal syncope. The intensity of suction to be employed in this study, that is -20 mmHg for 3 to 5 minutes, is very unlikely to induce presyncope. Should any signs of presyncope arise however (such as falling arterial blood pressure) the negative pressure will be switched off and recovery will be almost instantaneous.

FIT MEN AND WOMEN WANTED FOR SPACE TRAVEL RESEARCH

* IF YOU EXERCISE REGULARLY, CONSIDER YOURSELF HEALTHY AND AEROBICALLY FIT, ARE AGED BETWEEN 18 AND 45 AND WOULD LIKE TO EXPERIENCE *WEIGHTLESSNESS*, READ ON.

* We are looking for 8 fit individuals to act as subjects in a study designed to assess blood pressure control mechanisms on earth and in a weightless environment.

* All subjects will be exposed on 2 occasions to weightlessness on board European Space Agency parabolic flights.

* Subjects will, however, be required to cease from undertaking aerobic exercise and weight training for a period of 6 months between the parabolic flights.

* Before and after the '6 months no training' period subjects will undergo several procedures designed to assess their blood pressure control capabilities.

If you are interested in finding out more about this study please contact Simon Evetts at the Human Physiology Laboratory, King's College, London, on 0171 3334175 or at home on 0181 6772848.

IS 6 MONTHS REDUCED FITNESS WORTH A ONCE IN A LIFE TIME CHANCE OF EXPERIENCING WEIGHTLESSNESS ? YOU DECIDE !

REC Protocol Number .../.....

9b) SPECIAL GROUPS

PARTICIPATION OF WOMEN OF CHILD-BEARING AGE

In respect of this application:

a. Can women of child-bearing potential participate without significant risk?

Yes..✓.. No.....

b. Should women of child-bearing potential participate only in the presence of reliable contraception?

Yes..... No...✓..

c. Will women not of child-bearing potential be asked to participate?

Yes..✓.. No.....

Please justify your choice of statement.

No hazard to mother or embryo in early stages of pregnancy

An appropriate comment should be included in the consent form. Likewise, special consideration should be given to the position of lactating women.

CHILDREN UNDER 18 YEARS — N/A

Please describe how the children will be given a full understanding of what the study involves and how their freedom of choice will be ensured. If recruited from large groups how will peer pressure to conform be avoided.

Please attach letters to parents, teachers etc and any other documents used in recruitment.

10) DETAILS OF DRUGS OR PHARMACOLOGICALLY ACTIVE SUBSTANCES

Please state name, dose and duration of drugs or other substances to be administered, and the route of administration.

T-1824 Azovan Blue dye. 5 ml of 0.5% solution in saline to be injected intravenously on 8-10 separate occasions over 6-8 months period

Please state briefly the known pharmacology of the drugs and other pharmacologically or physiologically active substances, including possible side effects. Please provide appropriate documentation.

Martindale's Extrapharmacopoeia (31st ed., 1996) states "T-1824 (Azovan Blue) is a harmless, odourless blue dye which binds to plasma proteins. No toxic side effects are known. It may produce a transient slight blue discolouration of the skin in some subjects." It has been used routinely for over 40 years for the measurement of blood volume in healthy and ill subjects.

11) REGULATORY STATUS OF DRUGS

If the study involves the administration of drugs to patients, please indicate which of the following is applicable and append a copy of the relevant licence certificate (not applicable if a product licence is in force), or in the case of the exemptions, a copy of the letter from the Medicines Control Agency confirming exemption.

a) Product licence
b) Clinical trial certificate (CTC)
c) Clinical trial certificate exemption (CTX)
d) Doctors and Dentists Exemption Scheme (DDX)

The Committee will only give approval on presentation of the relevant certificate or letter confirming exemption (see Notes of Guidance).

12) INVASIVE PROCEDURES

If this study involves invasive procedures give a description of them, including the experience of the investigators in the use of the procedures. (An invasive procedure is defined as any procedure which disrupts tissues or organs of the body by piercing, cutting, temperature changes or exposure to electromagnetic radiation, or which introduces any instrument or measuring device into spaces or potential spaces within the body.)

An indwelling intravenous catheter will be placed in an anticubital vein and its potency maintained by periodic flushing with heparinised saline. 5 ml of 0.5% solution of T-1824 Azovan Blue dye will be injected through the catheter and six 5 ml aliquots of venous blood withdrawn for each estimation of blood volume [8-10 estimations over a 6-8 month period]. Venous pressure will also be recorded by means of the intravenous catheter and a pressure transducer during exposure to lower body suction. The placement of the catheter, injections, blood sampling and pressure recording will be performed by Prof. Ernsting who has had extensive experience of these procedures.

13) COMPENSATION

If this is a study in collaboration with a pharmaceutical company or an equipment manufacturer, please give the name of the company and indicate what arrangements exist for compensating patients or healthy volunteers for adverse effects resulting from their participation in the study (in most cases the Committee will only approve protocols if the pharmaceutical company involved confirms that it abides by ABPI guidelines).

N/A

A copy of the indemnification form should be submitted.

If this is a project undertaken for and on behalf of Kings College London the no-fault compensation scheme will operate (see guidelines).

14) IRRADIATION

Will subjects be exposed to ionising radiation in the course of this study?

Yes..... No.....✓

If yes please complete Appendix C. (Appendix C is only provided with the Notes on irradiation of human subjects)

15) DISCONTINUATION CRITERIA

Specify the conditions that would lead to a participant being discontinued from the study, or for the study to be terminated in part or as a whole.

1. At subject's request
2. In the event of exhibition of marked apprehension, dizziness, confusion, restlessness or symptons/signs of pre-syncope
3. Subject reports chest pain of dyspnoea
4. Abnormal form or arrhythmia in the electrocardiagram or abnormal blood pressure responses, other than those associated with the athletic heart syndrome
5. Failure of a significant item of monitoring or measuring equipment

16) DATA ANALYSIS

Is this a pilot study?

Yes..... No.....✓

If this is a multicentre study, please give brief details of other collaborating centres, etc.

European Space Agency - Jorge L Vago - Parabolic Flights Coordinator - microgravity flights in ESA Airbus A300 Zero G aircraft

Outline the statistical methods that will be used to analyze the data and state from whom statistical advice has been sought. In particular, state (if relevant) a) quantitative effect of treatment to be detected; b) statistical significance to be achieved; c) power of study:

Analysis of variance will be used to examine differences found in baroreceptor function during and following exposure to microgravity and detraining. Statistical significance will be assumed at a confidence level of 0.05

INFORMATION TO GENERAL PRACTITIONER

Please provide a copy of the letter which will be sent to the GP of all participating patients and healthy volunteers, and confirm that a copy of the protocol or suitable extracts thereof (subject information sheets) will be made available to healthy volunteers.

Letter to GP attached
All subjects will receive copies of the Subject Information Sheet and Consent Form

18) CONSENT AND INFORMATION FOR SUBJECTS

Please provide the text of the information sheet in Appendix A (below).

19) FILING AND STORAGE OF DOCUMENTS

Please indicate the time period for which you intent to store consent forms and other records:

.....5..... years.

Please state where the records will be stored:

Human Physiology Research Laboratory, King's College London (Kensington Campus)
.....

20) RESEARCH ETHICS COMMITTEE DECISION

Committee Decision .....

Meeting Date .....

Signed ..... (Chairman) Date .....

THIS PROTOCOL IS VALID FOR USE UNTIL .....

REC Protocol Number .../.....

APPENDIX A

KING'S COLLEGE MICROGRAVITY STUDY

SUBJECT INFORMATION SHEET

The purpose of this study is to investigate the control of blood pressure in highly trained individuals before and after a detraining period i.e. 6 months of no aerobic exercise, both at normal and zero gravity. The outline of the procedures that you will be involved in during the study can be seen below. Full details of all procedures are included overleaf.

At Kings College London:

2 Hrs
- Medical and fitness assessment.

3 Hrs
- Blood volume measurement.
- Baroreflex (blood pressure control reflex) assessment.

In a European Space Agency plane whilst weightless:

1 Day + Trvl
- Baroreflex assessment.

At Kings College London:

1 Day
- Baroreflex assessment.
- Venous pressure measurement.
- Forearm circumference measurement.
- 6 hours of head down tilt bed rest, followed by;
- Baroreflex assessment.
- Venous pressure measurement.
- Forearm circumference measurement.

Detraining Period:

6 Mon
- Approx 6 months of no aerobic exercise or weight training, during which:

2 Hrs
- Monthly fitness assessments.

2 Hrs
- Monthly blood volume measurements.

At Kings College London:

1 Day
- Baroreflex assessment.
- Venous pressure measurement.
- Forearm circumference measurement.
- 6 hours of head down tilt bed rest, followed by;
- Baroreflex assessment.
- Venous pressure measurement.
- Forearm circumference measurement.

At Kings College London:

2 Hrs
- Medical and fitness assessment.

3 Hrs
- Blood volume measurement.
- Baroreflex assessment.

In a European Space Agency plane whilst weightless:

1 Day + Trvl
- Baroreflex assessment.

At Kings College London:

1 Hr
- Final medical

Should you be interested in taking part in the study you will undergo a medical and fitness assessment. The medical examination will comprise the completion of a short health questionnaire and a physical examination of your cardiovascular and respiratory systems. The fitness test will consist of a treadmill maximal oxygen uptake test.

1. MAXIMUM OXYGEN UPTAKE TEST. This test is commonly known as a VO2max test and is used to obtain a quantifiable measure of your endurance capability. You will be asked to run on a treadmill for about 12 minutes. During this time your heart rate will be measured using a 3 lead ECG. After every 2 minutes of this period the speed of the treadmill will increase. During the test your expired air will be collected by means of a mouthpiece and tubing. You will be asked to continue running at increasing speeds until you reach volitional exhaustion. On your say the test will stop.

Providing your medical and fitness tests indicate that you are healthy and of a suitable level of fitness, and that you are able to void urine when at -6 degrees head-down tilt, you will be asked to act as a subject for the study. At this point you will have your blood volume measured as follows:

2. EVANS BLUE DYE TECHNIQUE. A small amount (5ml) of harmless, inert blue dye will be injected in to one of your arm veins whilst you recline on a couch. A catheter will be placed under local anaesthetic in an arm or hand vein. Small (5ml) blood samples will be drawn through the catheter after 10, 20, 30, 60, 90 and 120 minutes. The samples will enable the concentration of dye in your blood to be measured.

undergo further assessments

You will then return to the laboratory at a later date in order that the control of your blood pressure can be examined. This will be done under several circumstances, these being:

1. During passive standing.

2. During 25 seconds of weightlessness.

3. When lying horizontal.

4. When lying horizontal after 6 hours of 6 degree head down tilt.

Each of the above assessments will be repeated after a period of about 6 months during which you will cease from your normal exercise routine.

The procedures used to examine your blood pressure control mechanisms are as follows:

3. VALSALVA MANOEUVRE. This test involves you maintaining a pressure in a closed mouthpiece by an expiratory effort sustained for 15 seconds. Prior to, during and immediately after this manoeuvre your heart rate and blood pressure will be measured by means of a small cuff placed around one of your fingers. Should you feel any chest, neck or head pain, feel unduly dizzy, be unable to maintain the expiration or feel any indications of fainting, the manoeuvre will be discontinued.

You will perform the Valsalva's manoeuvre both in our laboratory in London and in a European Space Agency airplane during several periods of weightlessness. The weightlessness will be produced by the plane flying a parabolic manoeuvre. In between each period of weightlessness (microgravity) there will be period of normal gravity and increased gravity (macrogravity).

i. MICROGRAVITY. The periods of microgravity will last between 20 and 30 seconds. You will be exposed to about 20 such periods. During each you will float in the cargo bay of the plane and be asked to perform a Valsalva's manoeuvre. Microgravity causes a headward shift of body fluids and so you may feel a 'full' or congested feeling in your head. If you perform any 'acrobatics' when not being tested you may feel slightly nauseated. This form of motion sickness can be eased by staying still and moving the head slowly only when necessary.

ii. MACROGRAVITY. You will also be exposed to similar length periods of high gravity (up to about 3 times normal gravity) between each microgravity exposure. During these periods you will be sat stationary and will perform no tests. It is unlikely that you will feel any adverse effects other than very heavy limbs and head, however you will be shown some manoeuvres to perform should you start to feel faint during high G. These manoeuvres will help counter any adverse effects that may occur.

Approximately one week after the parabolic flight you will be asked to come to our laboratory again to perform several other procedures as laid out below.

4. NECK CHAMBER TECHNIQUE. This procedure involves placing a cuff around the front of your neck. The cuff is secured in place using velcro fasteners. Air will be blown in to and sucked from the cuff thus altering the pressure around your neck. The procedure is not uncomfortable. Several series of changing pressures will be applied whilst you hold an exhalation. Your blood pressure and heart rate will be monitored in the same manner as mentioned above. If at any time you feel uncomfortable or wish to stop this procedure the cuff will be removed.

5. LOWER BODY NEGATIVE PRESSURE (LBNP). The LBNP procedure is used to exert suction to a subject's lower body. You will be lying down on a couch. Your body from the waist down will be enclosed in an air tight chamber. Air will be sucked out from the chamber thus causing slight suction to be exerted on your lower body. You will feel a sensation similar to that of standing up suddenly. This is due to a shift of blood from the upper body to the lower body. The negative pressure will only be applied for about 3 to 5 minutes. During this time you should not feel any adverse effects, however if you do, the suction will be switched off and you will feel immediate relief.

For 20 minutes before, during and for 5 minutes after you will also undergo the following procedures simultaneously.

6. VENOUS OCCLUSION PLETHYSMOGRAPHY. Your left arm will have blood pressure cuffs placed just above the elbow and around the wrist. A small mercury filled rubber band will be placed around your forearm. The elbow cuff will be inflated for periods of 10 seconds. The wrist cuff will remain inflated for 3 to 5 minutes. You will not feel any discomfort. If you do, the cuffs will be adjusted. The elbow cuff inflation will be applied approximately 20 times. During each inflation the rubber/mercury band will record the circumference of the forearm.

7. CENTRAL VENOUS PRESSURE MEASUREMENT. When lying on either your back or right side your right arm will hang below the level of your body. A small catheter will have been placed in a vein on the inside of your elbow. This will be connected to some tubing. Venous pressure changes will be monitored using this apparatus during the course of the LBNP procedure.

After the LBNP test all apparatus except the catheter will be removed. You will then be asked to remain on the coach for 6 hours whilst at 6 degrees head down tilt.

8. HEAD DOWN TILT. This position will entail your head being slightly lower than your feet. Your blood pressure and heart rate will be measured every 15 minutes for the 6 hour period. You will not be able to get up, however receptacles will be provided should you wish to urinate. This period may lead to some congestion of the nose and sinuses and possibly some aching in the lower back towards the end.

After the head down tilt period procedures 4 to 7 will be repeated. You will then be monitored for 10 to 20 minutes to ensure you are fully recovered from the days tests and offered a meal. The day's experimentation should last about 8 hours in total.

All of the above procedures in the order shown will be repeated after a 6 month period during which you will refrain from exercising. Each month during this detraining period you will be asked to come back to the laboratory to perform a VO2max test and have your blood volume measured. After the detraining period you will be asked to perform Valsalva manoeuvres in the laboratory and for a second time during parabolic flight. After this second flight and after a final medical you will have finished all the practical tests in the study and will simply need to fill in several final questionnaires and forms.

You will no doubt have questions concerning the study and what is involved. If an appointment has not already been made at which we can discuss these issues, please call me, Simon Evetts, on 0171 3334175 to arrange a suitable time.

Finally, we are aware that all subjects will have to devote several days and quite allot of travel time to the study. Consequently your time will be reimbursed at a rate of £3.00/hour and all travel costs will be met.

Thank you for your time.

Simon N Evetts MSc BA (Hons)
PhD Student, King's College.

The College Research Ethics Committee has approved the above statement:

Signed .....(Chairman) Date .....

THIS INFORMATION SHEET IS VALID FOR USE UNTIL.....

APPENDIX B

REC Protocol Number .../.....

PARTICIPANT CONSENT FORM

Title of Project .....

The participant or key carer should complete the whole of this sheet himself/herself.

(Please cross out as necessary)

Have you been asked to consent for yourself or on behalf of someone else? Self/Other

If your answer to the above is "other", please give the name of the person for whom you are consenting. .....

Have you read the Information Sheet for Patients* and Healthy Volunteers? (This should normally be printed on the reverse side of this form.) Yes/No

Have you had an opportunity to ask questions and discuss this study? Yes/No

Have you received satisfactory answers to all of your questions? Yes/No

Have you received enough information about the study? Yes/No

Who have you spoken to? Dr/Mr/Ms .....

Do you understand that you are free to withdraw from the study at any time, without having to give a reason for withdrawing (and without affecting your future medical care)?* Yes/No

Do you agree to take part in this study? Yes/No

Have you declared your involvement in other research studies currently underway or undertaken in the last 12 months? Yes/No

Do you understand that you should not participate in this work if you become or are likely to become pregnant?* Yes/No

Signed ..... Date .....

(NAME IN BLOCK LETTERS) .....
(Relationship to the subject if not the participant: parent/guardian/other carer)

INVESTIGATOR'S STATEMENT

I confirm that I have carefully explained the nature, demands and foreseeable risks of the proposed study to the volunteer.

Signed ..... Date .....

NAME IN BLOCK LETTERS

(On completion a photocopy of this form and the information sheet should be given to the subject)

*delete or correct according to subject type

Appendix C
REC Protocol Number .../.....

APPENDIX C

Please answer the following questions in order to comply with the terms of the Ionising Radiation Regulations:

a) X-rays: Give details of any radiological exposures, eg conventional plain films, CT scans, etc., and state the radiation dose arising from i) the clinical procedure (if any) and ii) the research procedure.

Radiation dose arising from clinical procedure: mSv

Radiation dose arising from research procedure: mSv

b) Radioisotopes: Give details of the substances to be administered including their activities, state the registration number of the project with the local Radiation Protection Advisor, and state the date of expiry of the ARSAC approval. Also state the radiation dose arising from i) the clinical procedure (if any) and ii) the research procedure. (Please append a copy of the ARSAC Certificate.)

Radiation dose arising from clinical procedure: mSv

Radiation dose arising from research procedure: mSv

APPENDIX D

Letter to Family Practitioner

Dear Doctor,

Re: Name of Subject

Your patient has volunteered to take part in a study designed to investigate cardiovascular responses to microgravity before and after a 6 month period of detraining i.e. cessation of exercise.

The investigation is concerned with any differences that might exist between the trained and untrained state. A maximal treadmill stress test and measurements of blood volume will be required to be undertaken by all subjects. The blood volume measurements will necessitate venous samples to be taken.

The subjects will have their central venous pressure estimated by means of an indwelling venous catheter. They will have their baroreceptor function measured using the lower body neagative pressure method and a neck chamber technique. The neck chamber technique will involve brief periods (not more than 7 seconds) of suction and pressure being applied to the subjects neck. They will also have forearm blood flow measured which will involve placing blood pressure cuffs around their wrist (blown up to 200 mmHg for 5 minutes) and above the elbow (50 mmHg for 10 seconds).

Each subject will also be exposed to microgravity and macrogravity whilst on board an aircraft during parabolic flight. The weightless periods will last about 25 seconds as will the high gravity periods.

Your patient has agreed to participate in this study - if you know of any reason why he/she should not do so, such as a history of the presence of cardiovascular or respiratory disease, I would be grateful if you could inform me. It would be helpful if you could return the reply slip in the enclosed stamped, addressed envelope, as soon as you are able.

Thank you for your time.

Yours sincerely,

To:

Simon N Evetts
Human Physiology
King's College London
Cambden Hill
Kensington
London W8 7AH

I know of no reason why

.....

should not undertake a maximal exercise test, be exposed to microgravity and macrogravity, LBNP, neck pressure/suction assessment, passive head-down tilt or carry out Valsalva's manoeuvres (exhalation against moderate pressure).

His normal resting blood pressure values are ..... mmHg/ not known *.

* Delete where appropriate.

Signed: .....

Printed: .....

Date: .....

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SUBJECT SCREENING AND CONSENT FORMS

VOLUNTEER INFORMATION SHEET

NAME:_____ DOB: _____

Tel: _____

Fax:_____

Gender: M / F Occupation: _____

- Please list regular physical activities (e.g. running {what type}, weight-training, cycling, walking etc) together with how often, how long and at what standard you consider yourself to be at (personal fitness, club, county, national):

Activity	Frequency (per wk)	Duration	Level

- How long have you carried out regular exercise ? (circle)

More than 5 years Between 3 and 5 years Less than 3 years.

- Please list any medical conditions that you suffer from:

_____

_____

_____

_____

_____

- Do you smoke ? Yes / No

- If so how many of what per day ? _____

Please return this form in the envelope supplied

Form 1M *Date:*

QUESTIONNAIRE 1

- **Name:_____ I.D. Number :_____**
- **Age:_____**
- **Occupation :_____**

Please circle the appropriate response and comment where necessary....

- **Alcohol consumption** (amount) : average number of glasses or pints and type (wine, beer, spirits…)

  Per week : Type :

- **Do you smoke ?**
  - (Yes) (No)
  - If yes - average number of _____ per day _____.
- **Have you had any injuries in the last 6 months ?**
  - (Yes) (No)
  - If yes - specify :
- **Have you suffered any surgery in the last 6 months?**
  - (Yes) (No)
  - If yes - specify :
- **Have you ever been told by a medical doctor that you suffer from any disease / disorder ?**
  - (Yes) (No)

If 'Yes' please give details:

_____

_____

_____

- **Are you taking any prescribed / non- prescribed medication?**
  - ( ) Yes ( ) No
  - If yes, what type and dose?
- **Do you ever suffer from faints, dizziness or 'greying vision' ?**
  - ( ) Yes ( ) No
  - If 'Yes' please give details;

_____

_____

_____

_____

- **How often do you exercise each week ?**
  - ( )1 - 2 ( )3 - 4 ( )5 - 7
  - Type(s) of activity?_____
  - Duration of activity :_____ (hours)
  - Number of years you have been exercising regularly:.....years.
- **Do you know if you have relatives that suffer from :**

Disease		**Relationship (e.g. sister)**
( )	Heart problems	_____
( )	Hypertension	_____
( )	Diabetes	_____
( )	Asthma	_____
( )	High cholesterol	_____

- **Any other comments:**

_____

_____

_____

_____

ANALYSIS OF THE HAZARD OF CARBON MONOXIDE USE

1. 250 ml carbon monoxide (CO) escape in the laboratory housing the re-breathing circuit. The escape and perfect mixing of 250 ml of CO into the closed room (room volume = 56,000 l) would produce a concentration of:

$$\frac{0.25 \times 100}{56{,}000} = 0.00047\%$$

Threshold Limit Value for CO when working for 5 days/week for 8 hours/day is 0.005% (HSE EH40). Therefore, as the escape of 250ml of CO produces only one tenth of the concentration recognised as the maximum allowable value for chronic exposure to CO, this eventuality does not present any serious risk to people in the room.

2. Maximum CO possible in human circulatory system. Human blood can carry approximately 20 ml CO per 100ml. Assuming a blood volume of 5.5 l for the average sized male then when fully saturated with CO the blood would contain:

$$200 \times 5.5 = 1100\text{ml CO.}$$

3. Direct addition of 75 ml CO to the subject. If a 75 ml sample of CO were added directly to the subject's blood their carboxyhaemoglobin (HbCO) concentration would rise by:

$$\frac{75 \times 100}{1100} = 6.8\%\ \text{HbCO}$$

Regular smokers can often achieve HbCO levels of 10%. Normal functioning is possible with levels up to 20%. Close to or above 40% can lead to collapse during physical exertion (Boothby 1954). Therefore, an absolute increase of 6.8% from normal levels for a non-smoker (usually 0 to 1%) is not hazardous. Smokers were not involved with this study either as subjects or investigators.

4. Direct inhalation of 250 ml CO. A serious leak of the sample bag in the presence of the investigator or subject may mean high localised concentrations rather than a perfect mixing as shown in example 1.0 above. Since the absorption of 75 ml of CO will produce a 6.8% rise in HbCO then absorption of 250 ml (the greatest amount of CO that will be able to be inhaled from a local high concentration) will lead to an HbCO concentration of:

$$3.33 \times 6.8 = 22.6\%$$

It is generally recognised that the threshold for serious effects of CO poisoning is a HbCO level is 40%. Therefore, a worst case scenario in which someone directly breathes the entire contents of the 250 ml sample bag containing pure CO would not result in a direct or immediate risk to life.

Safety Precautions:

- A distance of at least 2 m from the investigator or subject was used for CO/waste gas venting to ambient.
- A fan was angled to blow air away from the subject and investigator so that in the unlikely event of a CO leak the gas would be blown away from the experimental area.
- A cylinder of 100% oxygen coupled to an ambubag was at hand in the event of an emergency (Henderson 1938). Oxygen would have been administered in the event of signs of:
    - dizziness
    - drowsiness
    - loss of consciousness

KING'S COLLEGE MICROGRAVITY STUDY SUBJECT INFORMATION & POSTER

The purpose of this study is to investigate the control of blood pressure in highly trained individuals before and after a detraining period i.e. 3 months of no aerobic exercise, both at normal and zero gravity. The outline of the procedures that you will be involved in during the study can be seen below. Full details of all procedures are included overleaf.

Procedure & Location	**Duration**
At Kings College London:	
- Medical and fitness assessment.	2 hrs
- Blood volume measurement.	3 hrs
- Baroreflex (blood pressure control reflex) assessment.	
In a European Space Agency aircraft whilst weightless:	1day + travel
- Baroreflex assessment.	
At Kings College London:	
- Baroreflex assessment.	1 day
- Venous pressure measurement.	
- Forearm circumference measurement.	
- 6 hours of head down tilt bed rest, followed by,[22]	
- Baroreflex assessment.	
- Venous pressure measurement.	
- Forearm circumference measurement.	
Detraining Period:	
- Approx 3 months of no aerobic exercise or weight training, during which:	
- Monthly fitness assessments.	2 hrs
- and monthly blood volume measurements will be taken.	2 hrs
At Kings College London:	
- Baroreflex assessment.	1 day
- Venous pressure measurement.	
- Forearm circumference measurement.	
- 6 hours of head down tilt bed rest, followed by,	
- Baroreflex assessment.	
- Venous pressure measurement.	
- Forearm circumference measurement.	
At Kings College London:	
- Medical and fitness assessment.	2 hrs
- Blood volume measurement.	3 hrs
- Baroreflex assessment.	
In a European Space Agency plane whilst weightless:	1 day + travel
- Baroreflex assessment.	
At Kings College London:	
- Final medical	1 hr

[22] Subsequently this element of the study was dropped.

Should you be interested in taking part in the study you will undergo a medical and fitness assessment. The medical examination will comprise the completion of a short health questionnaire and a physical examination of your cardiovascular and respiratory systems. The fitness test will consist of a treadmill maximal oxygen uptake test.

1. MAXIMUM OXYGEN UPTAKE TEST. This test is commonly known as a VO_2max test and is used to obtain a quantifiable measure of you endurance capability. You will be asked to run on a treadmill for about 12 minutes. During this time your heart rate will be measured using a 3 lead ECG. After every 2 minutes of this period the speed of the treadmill will increase. During the test your expired air will be collected by means of a mouthpiece and tubing. You will be asked to continue running at increasing speeds until you reach volitional exhaustion. On your say the test will stop.

Providing your medical and fitness tests indicate that you are healthy and of a suitable level of fitness, and that you are able to void urine when at -6 degrees head-down tilt, you will be asked to act as a subject for the study. At this point you will have your blood volume measured as follows:

2. CARBON MONOXIDE BLOOD VOLUME MEASUREMENT. A very small amount of carbon monoxide will be added to a closed system containing oxygen. You will be asked to breath from this system for 10 minutes. In addition to carrying out this procedure a small finger pin-prick blood sample will be taken to measure your haemoglobin level.

You will then undergo further assessments at a later date to examine the control of your blood pressure. This will be done under several circumstances, these being:

1. During several 25 second periods of weightlessness.
2. When lying horizontal.
3. When lying horizontal at 6 degree head down tilt.

Each of the above assessments will be repeated after a period of about 3 months during which you will cease from your normal exercise routine.

You will carry out the following procedure designed to examine your blood pressure control mechanisms:

3. VALSALVA MANOEUVRE. This test involves you maintaining a pressure in a closed mouthpiece by an expiratory effort sustained for 10-15 seconds. Prior to, during and immediately after this manoeuvre your heart rate and blood pressure will be measured by means of a small cuff placed around one of your fingers. Should you feel any chest, neck or head pain, feel unduly dizzy, be unable to maintain the expiration or feel any indications of fainting, the manoeuvre will be discontinued.

You will perform the Valsalva's manoeuvre in our laboratory in London and in a European Space Agency aircraft during several periods of weightlessness. Each experiment will be carried out approximately 5 times. The weightlessness will be produced by the plane flying a parabolic manoeuvre. In between each period of weightlessness (microgravity) there will be period of normal gravity and increased gravity (macrogravity).

a. MICROGRAVITY. The periods of microgravity will last between 20 and 30 seconds. You will be exposed to about 30 such periods. During each you will sit in the passenger bay of the aircraft and be asked to perform a Valsalva's manoeuvre. Microgravity causes a head ward shift of body fluids and so you may feel a 'full' or congested feeling in your head. If you perform any

'acrobatics' when not being tested you may feel slightly nauseated. This form of motion sickness can be eased by staying still and moving the head slowly only when necessary.

b. MACROGRAVITY. You will also be exposed to similar length periods of increased gravity (up to about 2 times normal gravity) between each microgravity exposure. During these periods you will be sat stationary and will perform no tests. It is unlikely that you will feel any adverse effects other than very heavy limbs and head, however you will be shown some manoeuvres to perform should you start to feel faint during high G. These manoeuvres will help counter any adverse effects that may occur.

Approximately one week after the parabolic flight you will be asked to come to our laboratory again to perform the procedures as laid out below.

3. VALSALVA MANOEUVRE. As previously mentioned.

4. LOWER BODY NEGATIVE PRESSURE (LBNP). The LBNP procedure is used to exert suction to a subject's lower body. You will be lying down on a couch. Your body from the waist down will be enclosed in an air tight chamber. A slight suction will be applied to your lower body. You will feel a sensation similar to that of standing up suddenly. This is due to a shift of blood from the upper body to the lower body. The negative pressure will only be applied for about 3 to 5 minutes. During this time you should not feel any adverse effects, however if you do feel any dizziness or discomfort the suction will be switched off and you will feel immediate relief.

For 20 minutes before, during and for 5 minutes after you will also undergo the following procedures simultaneously.

5. VENOUS OCCLUSION PLETHYSMOGRAPHY. Your arm will have blood pressure cuffs placed just above the elbow and around the wrist. A small mercury filled rubber band will be placed around your forearm. The elbow cuff will be inflated for periods of 10 seconds. The wrist cuff will remain inflated for 3 to 5 minutes. You will not feel any discomfort. If you do, the cuffs will be adjusted. The elbow cuff inflation will be applied approximately 20 times. During each inflation the rubber/mercury band will record the circumference of the forearm.

6. PERIPHERAL VENOUS PRESSURE MEASUREMENT. When lying on either your back or side your arm will hang below the level of your body. A small catheter will have been placed in a vein on the inside of your elbow. This will be connected by tubing to a transducer and recorder for venous pressure measurement. Venous pressure changes will be monitored using this apparatus during the course of the LBNP procedure.

AFTER 3 MONTHS DETRAINING. All of the above procedures in the order shown will be repeated after a 3 month period during which you will refrain from exercising. Each month during this detraining period you will be asked to come back to the laboratory to perform a VO_2max test and have your blood volume measured. After the detraining period you will be asked to perform Valsalva manoeuvres in the laboratory and for a second time during parabolic flight. After this second flight and after a final medical you will have finished all the practical tests in the study and will simply need to fill in several final questionnaires and forms.

Although all techniques used in this study have been tested and validated and are known to be safe, I would like nevertheless to assure you that in the event of your suffering any adverse effects shown to be as a consequence of your participation in this study you may be compensated through the King's College London 'No-Fault' Compensation Scheme.

You will no doubt have questions concerning the study and what is involved. If an appointment has not already been made at which we can discuss these issues, please call me, Simon Evetts, on 0171 3334175 to arrange a suitable time.

Finally, we are aware that all subjects will have to devote several days and quite allot of travel time to the study. Consequently you will receive appropriate reimbursement for your time and travel costs.

Thank you.

Simon N Evetts BA(Hons) MSc
PhD Student, King's College.

NB. Certain aspects of the study as outlined above e.g. 6 hours head-down tilt, were dropped subsequent to the production of this information sheet.

SUBJECT RECRUITMENT POSTER

FIT MEN AND WOMEN WANTED FOR SPACE TRAVEL RESEARCH !

IF YOU EXERCISE REGULARLY, CONSIDER YOURSELF HEALTHY AND AEROBICALLY FIT, ARE AGED BETWEEN 18 AND 45 AND WOULD LIKE TO EXPERIENCE REAL *WEIGHTLESSNESS*, READ ON. . .

- We are looking for 8 very fit individuals to act as subjects in a study designed to assess blood pressure control mechanisms on earth and in a weightless environment.

- All subjects will be exposed to about 20 periods of weightlessness on 2 occasions on board European Space Agency parabolic flights.

- Subjects will, however, be required to cease from undertaking aerobic exercise and weight training for a period of about 3 months between the parabolic flights.

- Before and after the '3 months of no training' subjects will undergo several procedures designed to assess their blood pressure control capabilities. A full day on several occasions will be needed from each subject for these experiments. All expenses incurred will be reimbursed.

If you are interested in finding out more about this study please contact **Simon Evetts** at the Human Physiology Laboratory, King's College, London, on **0171 3334175** or **Prof John Ernsting** on **3334176.**

KCL Research No. 95/96-66

APPENDIX E

ASSESSMENT OF CARBON MONOXIDE ANALYSER LINEARITY AND CLOSED-CIRCUIT CARBON MONOXIDE EQUILIBRATION

Assessment of the linearity of the response of the carbon monoxide analyser and speed of mixing of gases in the breathing circuit was conducted in preparation for the measurement of blood volume by means of the carbon monoxide rebreathing technique. Air and a mixture of 0.3% carbon monoxide and nitrogen were mixed to produce 500ml of gas with a carbon monoxide concentration of 0.029%. The gas was contained within an anaesthetic bag. The gas within the bag was re-cycled through a PK Morgan carbon monoxide analyser for continuous measurement of carbon monoxide concentration (Fig E1).

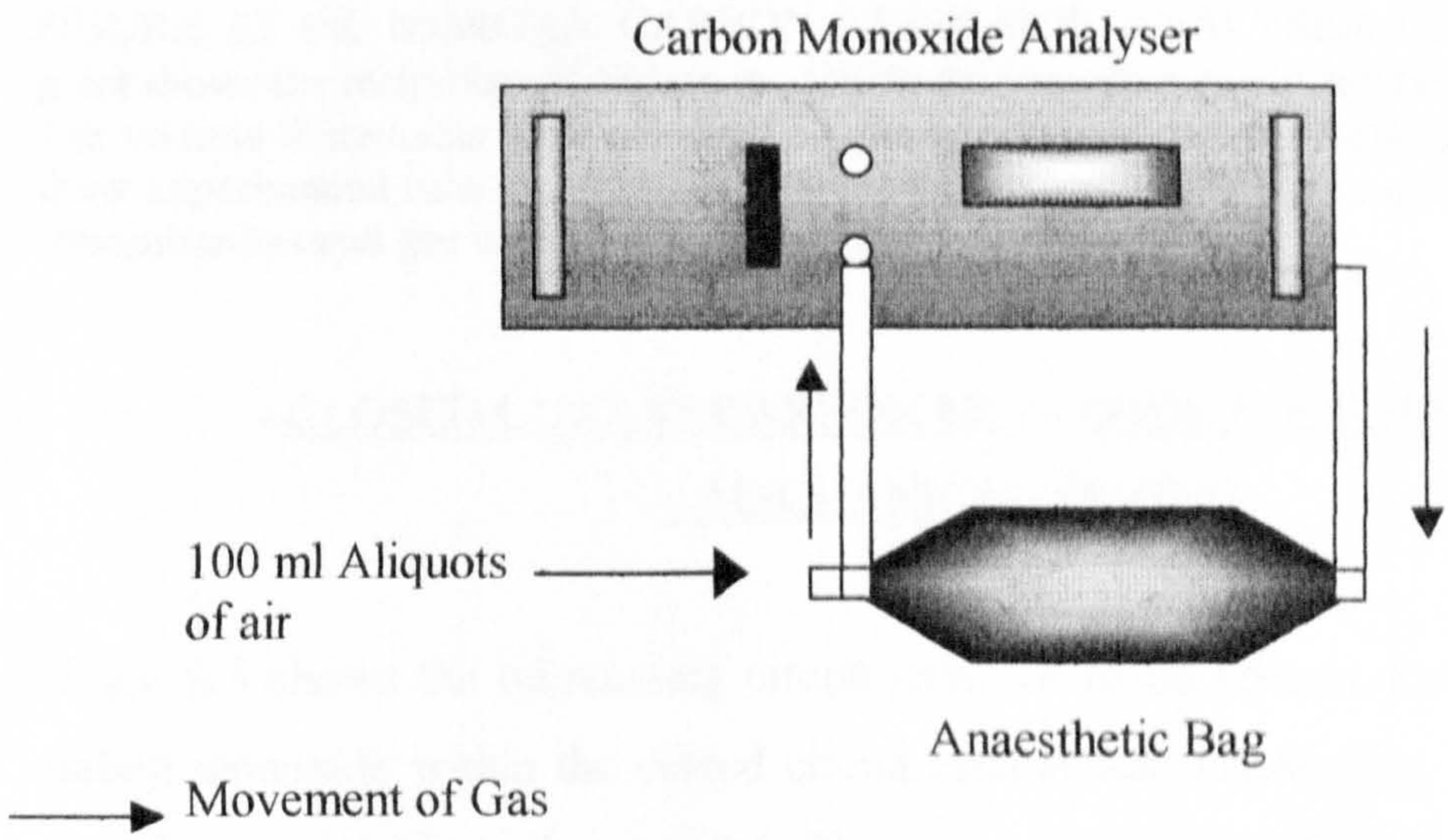

FIGURE E.1. CARBON MONOXIDE ANALYSER LINEARITY ASSESSMENT APPARATUS

100ml of air was added to the bag using a 50ml syringe. The bag was agitated for 2 – 3 min to aid mixing of the gas. The gas was continuously cycled through the analyser and returned to the anaesthetic bag thus providing a continuous reading of carbon monoxide concentration. When the concentration reading remained stable for more than 30 s the value was recorded for the new bag volume. This procedure was continued until a three to four fold increase in bag volume was achieved. The reciprocal of carbon monoxide concentration was then plotted against volume as an analysis of analyser linearity. Figure E.2 shows two examples of such linearity assessments. Correlation coefficients of 0.999 indicate that analysis was highly reliable for this machine.

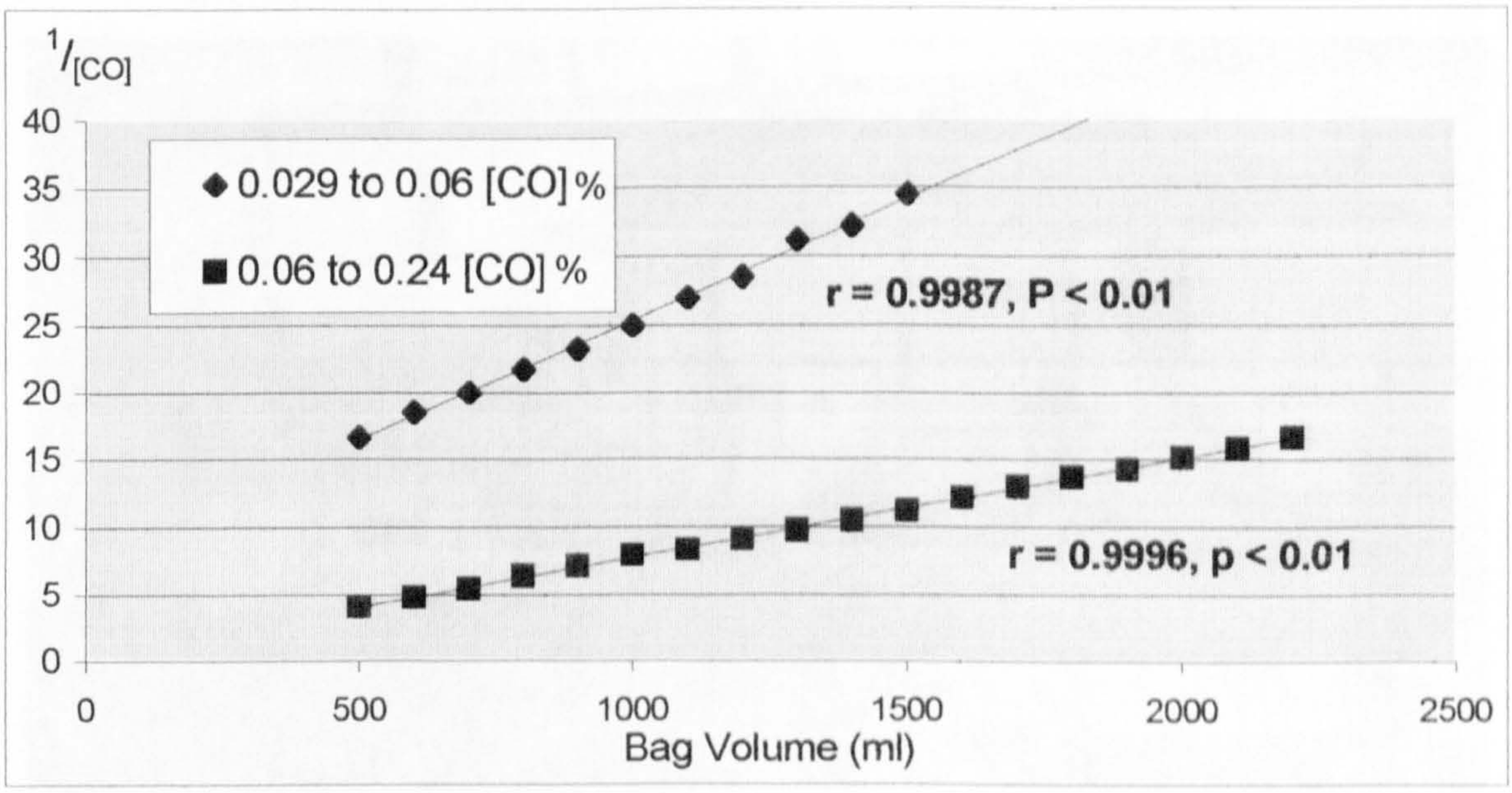

FIGURE E2 PK MORGAN CARBON MONOXIDE ANALYSER LINEARITY. Each data point shows the reciprocal of carbon monoxide concentration measured for a specific gas volume. The volume increments were achieved by the addition of 100ml aliquots of air. The two plots show experimental runs in which the relationship between different ranges[22] of carbon monoxide concentrations and gas volume was examined.

CLOSED CIRCUIT CARBON MONOXIDE EQUILIBRATION – MECHANICAL MIXING

Figure E.3 shows the rebreathing circuit used for blood volume analysis. The mixing of carbon monoxide within the closed circuit system was assessed by the addition of 15ml of carbon monoxide to the circuit (5.2l volume) containing 98% oxygen. The gas within the circuit was continuously circulated through the carbon monoxide analyser. The 15ml aliquot of carbon monoxide was added to the circuit at a point in the main circle of tubing (A). The gas was circulated by the use of an ambu-bag attached at point B (1 l ambu-bag at a compression rate of 10 $l.min^{-1}$). Figure E.4 shows the carbon monoxide concentrations measured over 10 min for three runs, each using 15ml carbon monoxide within a 98% oxygen circuit.

[22]In the region of those concentrations used during blood volume analysis.

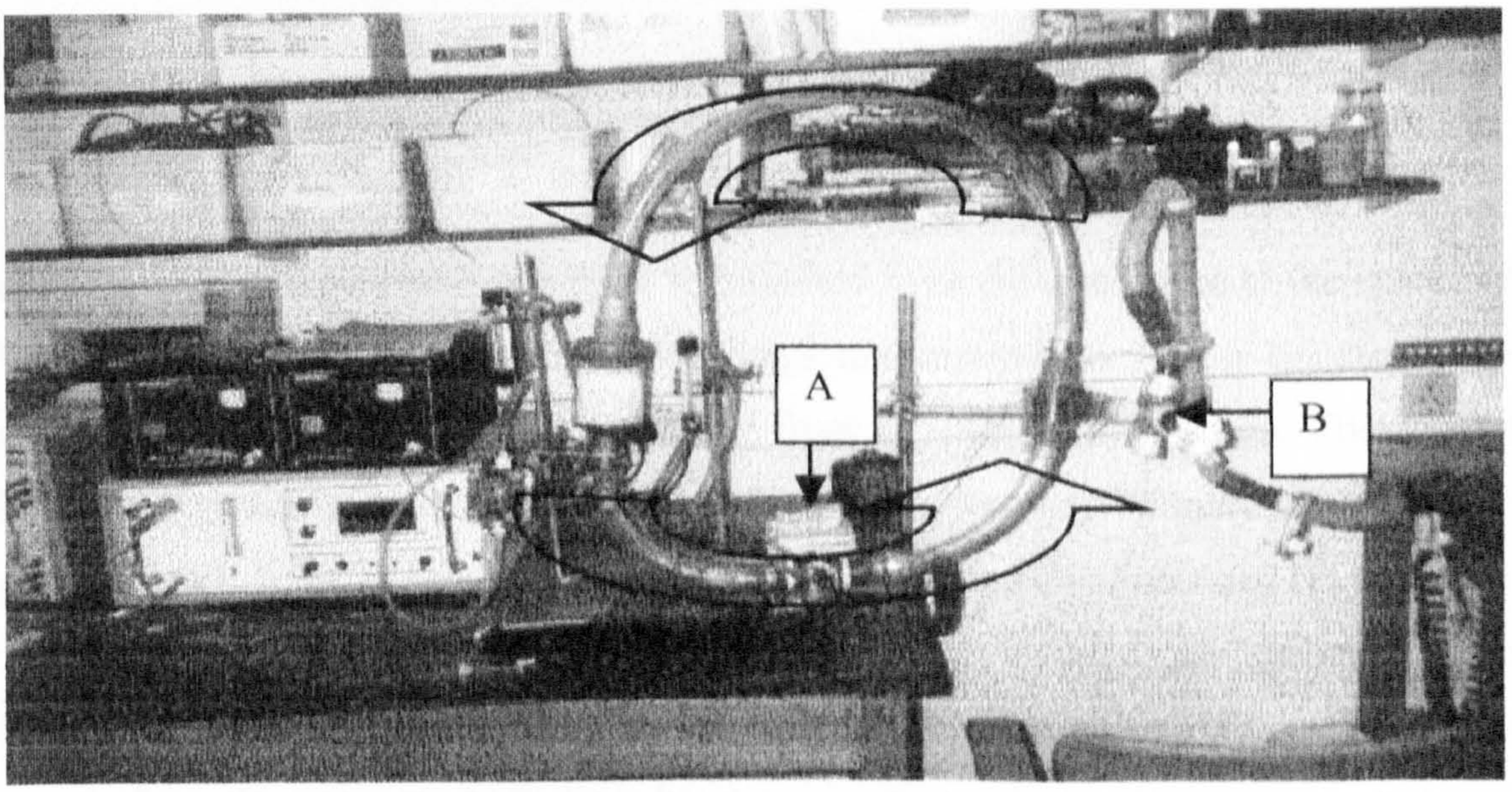

FIGURE E3 CLOSED CIRCUIT REBREATHING SYSTEM. Aliquots of carbon monoxide were added at point A. Compression and re-inflation of a rubber bag at point B enabled mixing of gas within the circuit. Hollow arrows indicate direction of movement of air.

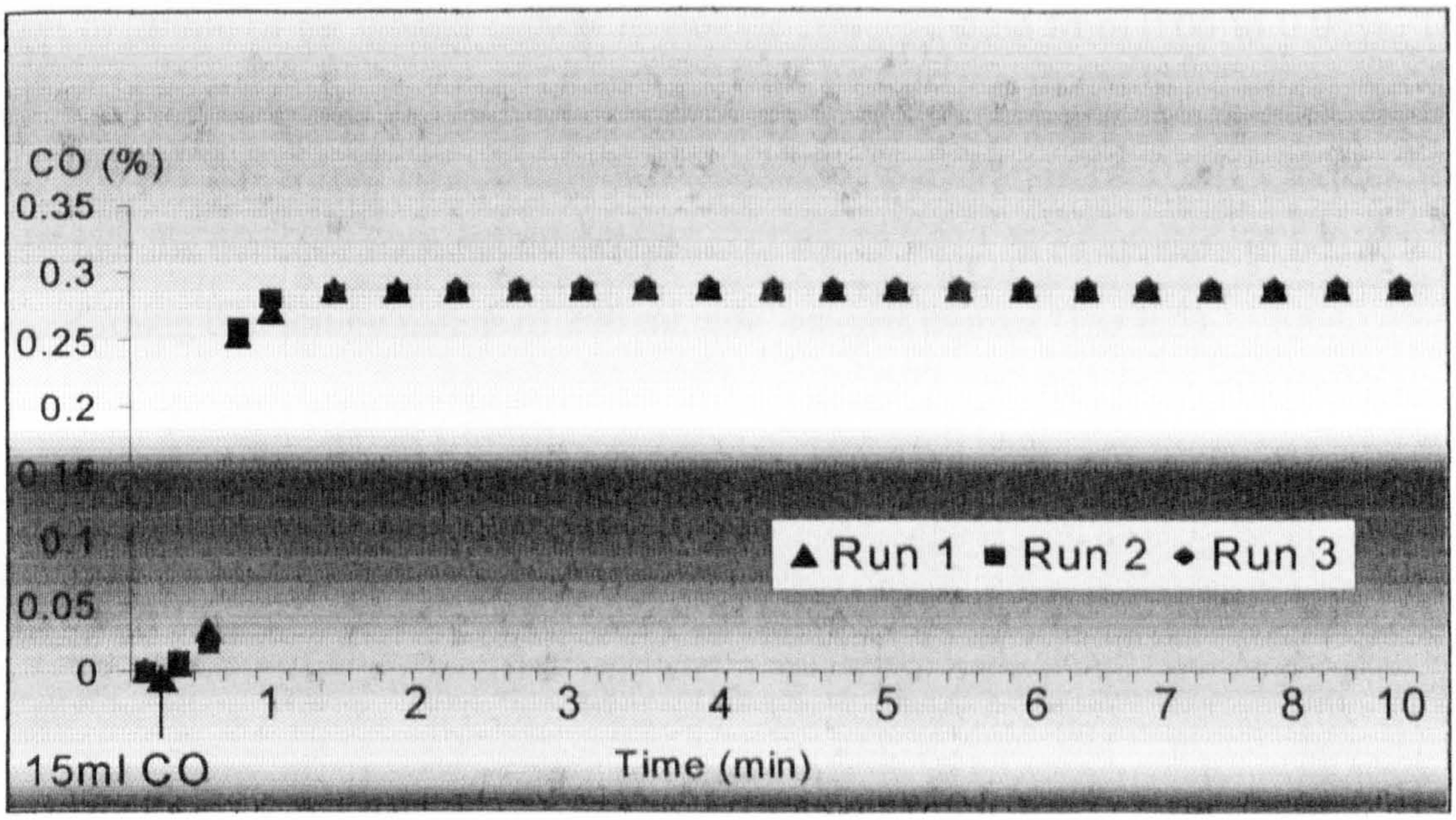

FIGURE E4 CLOSED CIRCUIT SYSTEM - CARBON MONOXIDE EQUILIBRATION. Equilibration within the circuit occurred within 2 min in each case.

CLOSED CIRCUIT CARBON MONOXIDE EQUILIBRATION – HUMAN MIXING.

Equilibration was slower when a subject re-breathed from the circuit due to the uptake of carbon monoxide from the system by the lungs and circulation. Figure E5 shows the equilibration curve for a subject re-breathing from the system for 10 min. The subject had previously breathed 100% oxygen for 10 min to remove nitrogen from the respiratory tract. 50ml of carbon monoxide was added at the time indicated by the arrow on the figure. The concentration of carbon monoxide was continuously measured for a further 10 min after the subject came off the system. The very gradual dilution of carbon monoxide from the point at which the subject came off the circuit (25 min) was attributed to the oxygen inflow set at the subjects' basal oxygen uptake (~ 200 $ml.min^{-1}$) which was inadvertently left on. The results of the linearity experiment (Fig E.2) show that for a volume of about 750ml (anaesthetic bag, analyser circuit and associated tubing) the addition of 200ml of air diluted carbon monoxide concentration from 0.06 to 0.05%. The complete rebreathing circuit (5l) was 6.6 times this volume and thus the addition of 200 $ml.min^{-1}$ of oxygen would reduce carbon monoxide concentration by 0.0015 $\%.min^{-1}$ i.e. over 10 min the concentration would decrease by about 0.015 % as appears to be the case thus confirming dilution by means of 200 $ml.min^{-1}$ oxygen ingress (Fig E.5).

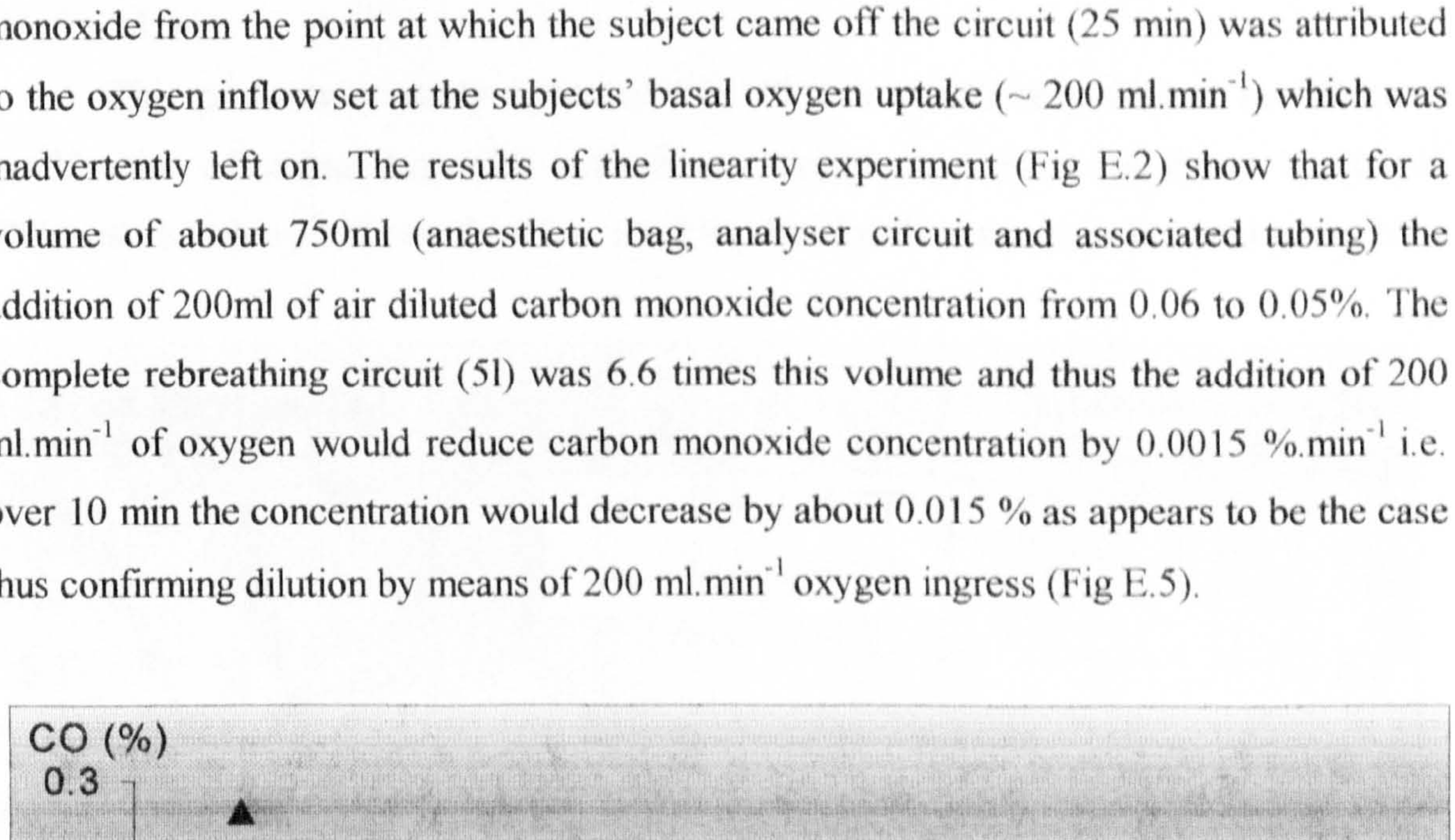

FIGURE E5 CLOSED CIRCUIT SYSTEM - CARBON MONOXIDE EQUILIBRATION - SUBJECT JE RE-BREATHING

Further analysis of the duration required for adequate carbon monoxide equilibration between the circuit and the subject was undertaken using different subjects. Each subject re-breathed from 2 bags attached to the circuit during the course of one blood volume measurement. Rebreathing from the first bag enabled a baseline carbon monoxide concentration to be ascertained. The second bag involved re-breathing for 10 to 15 min after an aliquot of carbon monoxide had been introduced into the circuit. The subject was then turned back in to the first bag (now re-filled with oxygen [23]) for a further 6 min to confirm the carbon monoxide concentration measured in the second.

Figure E6 shows the circuit carbon monoxide concentrations during the re-breathing of two subjects. One subject re-breathed from the second bag for 13 min and one for 15 min.

This preliminary study indicated that 15 min would be sufficient for adequate equilibration of carbon monoxide between the circuit and subject (as shown by subject TR's results below) and was therefore used for the blood volume measurement protocol.

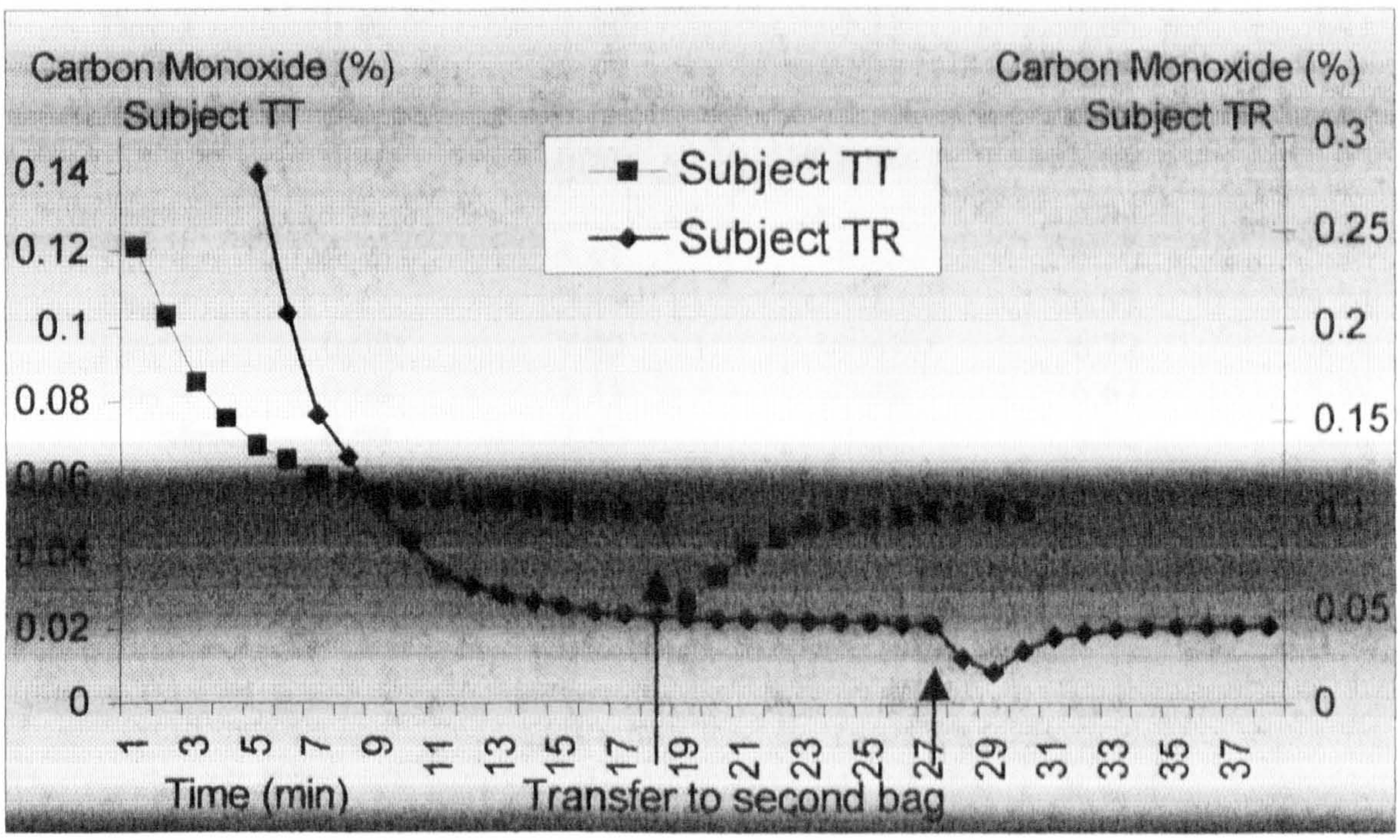

FIGURE E6 CLOSED CIRCUIT SYSTEM - CARBON MONOXIDE EQUILIBRATION. The dilution curves show the carbon monoxide equilibration of two subjects re-breathing on the blood volume measurement circuit. The transfer of the subject from one anaesthetic bag to the second (containing 2000ml of 98% oxygen) produced transient reductions in circuit carbon monoxide concentration as shown.

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[23]Which produced a negligible degree of dilution.

THE RELIABILITY OF BLOOD VOLUME MEASUREMENT USING THE CARBON MONOXIDE REBREATHING TECHNIQUE

Blood volume was measured 4 times for two subjects using the carbon monoxide rebreathing technique outlined in the methods chapter of this thesis. The subjects undertook the procedure at different times of the day on 4 separate days during one week. During the week the subjects maintained normal daily routine which did not include the intake of large amounts of alcohol or any other fluids or strenuous exercise.

Table E.1 shows the baseline, experimental (after carbon monoxide administration) carboxyhaemoglobin alveolar concentrations, change in concentration and calculated blood volumes for each measurement.

	Carboxyhaemoglobin Concentration, %				**Blood Volume,**
	Baseline	Experimental 1	Experimental 2	Change	Litres
Subject JE					
Day 1	0.67	6.92	6.92	6.58	5.47
Day 2	0.67	7.15	7.07	6.48	5.55
Day 3	0.80	7.45	7.23	6.65	5.41
Day 4	0.68	7.34	7.35	6.66	5.40
Mean	**0.71**	**7.22**	**7.14**	**6.59**	**5.46**
± SD	**0.06**	**0.23**	**0.19**	**0.08**	**0.07**
Subject DS					
Day 1	0.46	6.81	6.75	6.36	5.36
Day 2	0.57	7.44	7.52	6.87	5.24
Day 3	0.68	7.40	7.47	6.72	5.36
Day 4	0.68	7.35	7.42	6.67	5.39
Mean	**0.60**	**7.25**	**7.29**	**6.66**	**5.34**
± SD	**0.11**	**0.30**	**0.36**	**0.21**	**0.07**

TABLE E.1. CARBOXYHAEMOGLOBIN AND BLOOD VOLUME MEASUREMENTS FROM FOUR ASSESSMENTS OF BLOOD VOLUME OF TWO SUBJECTS. Baseline values were obtained from the first period of rebreathing; Experimental 1 from the second period (immediately after carbon monoxide administration) and Experimental 2 from the third and final (confirmatory) rebreathing period.

The maximum difference between any two measures of change in carboxyhaemoglobin were 0.18% and 0.31% for subjects JE and DS respectively. The maximum difference between any two measures of blood volume for each subject was 150 ml and a blood volume measurement within ± 69 ml can be assumed for a 95% confidence interval. This level of accuracy was accepted as appropriate for the detection of blood volume changes resulting from altered endurance fitness which should be in the region of 10 – 20% or 550 to 1100 ml for a blood volume of 5.5 l.

CALCULATION OF BLOOD VOLUME AND AN EXAMPLE OF SPECTROPHOTOMETER CALIBRATION CURVE.

The basis of the method is to measure the increase in the concentration of carboxy-haemoglobin ([HbCO]) in the blood produced by a known dose of carbon monoxide (CO) introduced into a closed breathing circuit filled with 100% oxygen. The [HbCO] in the blood before and after the administration of CO is estimated from the equilibrium concentrations of CO in the closed circuit prior to and after the addition of CO.

CALCULATIONS OF [HBCO] IN THE BLOOD

The [HbCO] in the blood is calculated from the equilibrium concentration of CO in the circuit which is equal to that in the alveolar gas (F_ACO_2) and the concentration of oxygen in the alveolar gas (F_AO_2) The latter is obtained from the Fo_2 in the inspired gas (1.0) and the end-tidal concentration of carbon dioxide (F_AO_2) measured during the last minute of the equilibration period using the appropriate form of the alveolar gas equation

$$F_AO_2 = F_IO_2 - F_ACO_2$$

The Haldane equation states that:

$$\frac{[HbCO]}{[HbO_2]} = M \times \frac{PCO}{PO_2} = M \times \frac{F_ACO}{F_AO_2} \quad -(1)$$

where M is the Haldane constant.

The concentration of haemoglobin in the blood flowing from the pulmonary capillaries will be negligible as the subject is breathing 100% oxygen so that

$$[HbO_2] = [1 - HbCO]$$

Substituting this expression for $[HbO_2]$ in equation 1 gives

$$\frac{[HbCO]}{[1\text{-}HbCO]} = M \times \frac{F_ACO}{F_AO_2} \quad -(2)$$

which can be rearranged to give equation 3

$$[HbCO] = \frac{M \times \frac{F_ACO}{F_AO_2}}{1 + M \times \frac{F_ACO}{F_AO_2}} \quad -(3)$$

CALCULATION OF BLOOD VOLUME

The difference between the [HbCO] in the blood before and after the addition of a known volume of CO to the closed circuit and hence absorbed into the blood [the quantity of CO remaining in the gas in the closed circuit and lungs is negligible] depends upon the total quantity of haemoglobin in the blood.

Since the carbon monoxide capacity of haemoglobin is 1.390 ml STPD of CO per gramme of haemoglobin, the relationship between the quantity of CO added to the blood (Vco) and the consequent increase in the concentration of HbCO (expressed as a percentage of the CO capacity of the blood) will be

$$\text{Change in [HbCO]} = \frac{\text{VCO x 100}}{\text{Total Hb x 1.39}}$$

Whence

$$\text{Total Body Haemoglobin} = \frac{\text{VCO x 100}}{\text{Change in [HbCO]x 1.39}}\ \text{g}$$

The blood volume is then calculated from the total quantity of haemoglobin and the concentration of haemoglobin in the blood determined from the venous blood sample assuming that the whole body haematocrit equals that of the venous blood sample

$$\textbf{Blood volume (litre)} = \frac{\text{Total Haemoglobin (g)}}{\text{Haemoglobin concentration (g/l)}}$$

EXAMPLE OF A SPECTROPHOTOMETER CALIBRATION CURVE

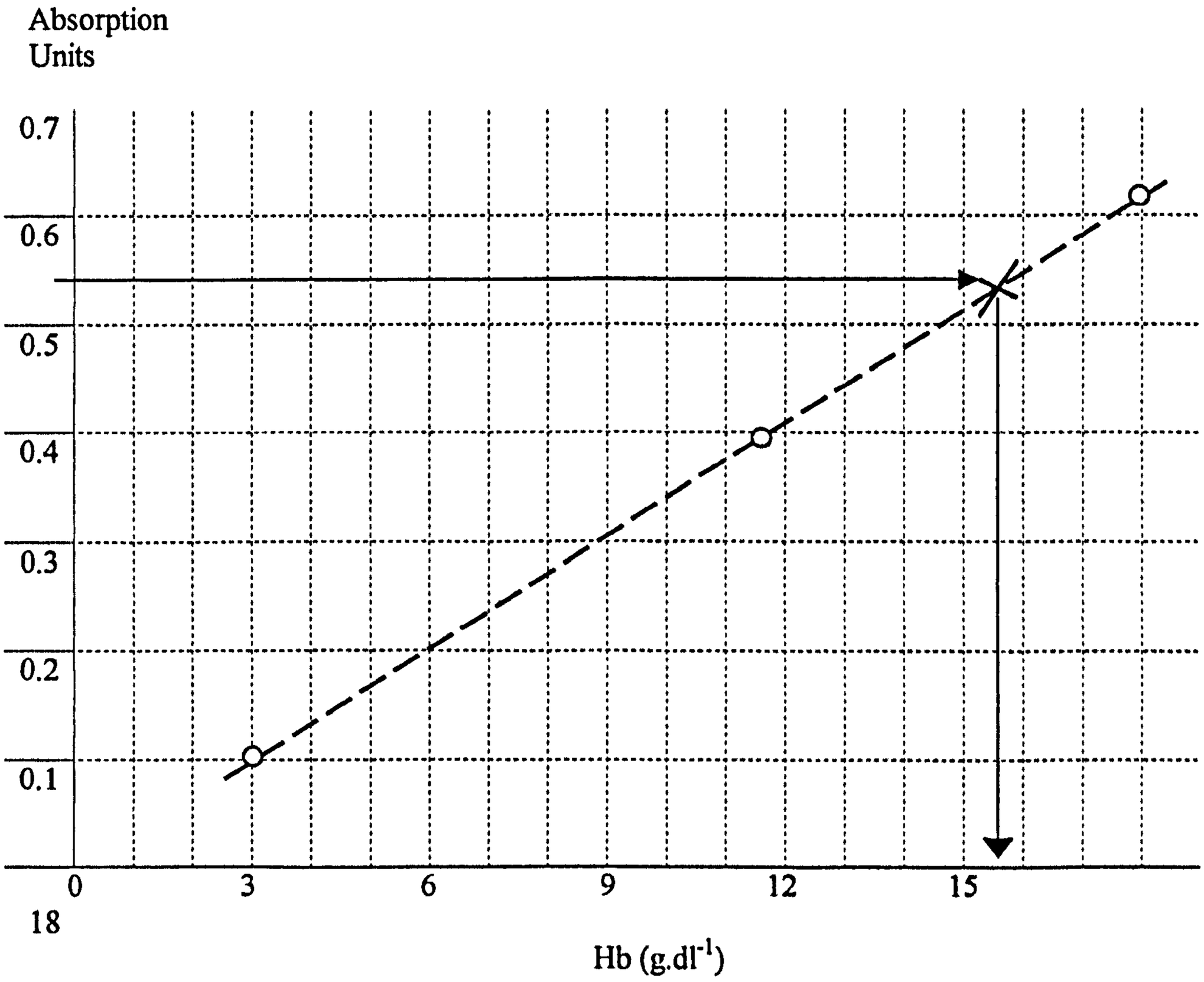


FIGURE F1. EXAMPLE OF A HAEMOGLOBIN CONCENTRATION READING

A set of axis with 0.1g.dl^{-1} and 0.005 Absorption Unit graticules were printed on the reverse of each subject's blood volume record sheet. The three measurements of absorption units (each a mean of 3 measures) were taken for the three standards and used to plot a calibration curve as shown above. The reading for the subject's Drabkin's/blood sample was then read from this relationship.

APPENDIX G

CALCULATION OF HALDANE'S AFFINITY RATIO

The partial pressure of carbon monoxide required to saturate haemoglobin is approximately 1/200 to 1/300 of that of oxygen (Boothby, 1954). This ratio of affinity of blood for carbon monoxide is commonly annotated as 'M' (Haldane's constant) in the equation:

$$\frac{[HbCO]}{[HbO_2]} = M \frac{PCO}{PO_2} \qquad (1)$$

Where [HbCO] and [HbO_2] represent the number of moles of carbon monoxide and oxygen combined with 1 litre of blood and PCO and PO_2 represent the partial pressures of the relevant gases. Figure G1 illustrates the similarity of the shapes of the oxygen and carbon monoxide dissociation curves when a. Hb, O_2 and HbO_2 and b. Hb, CO and HbCO only are present.

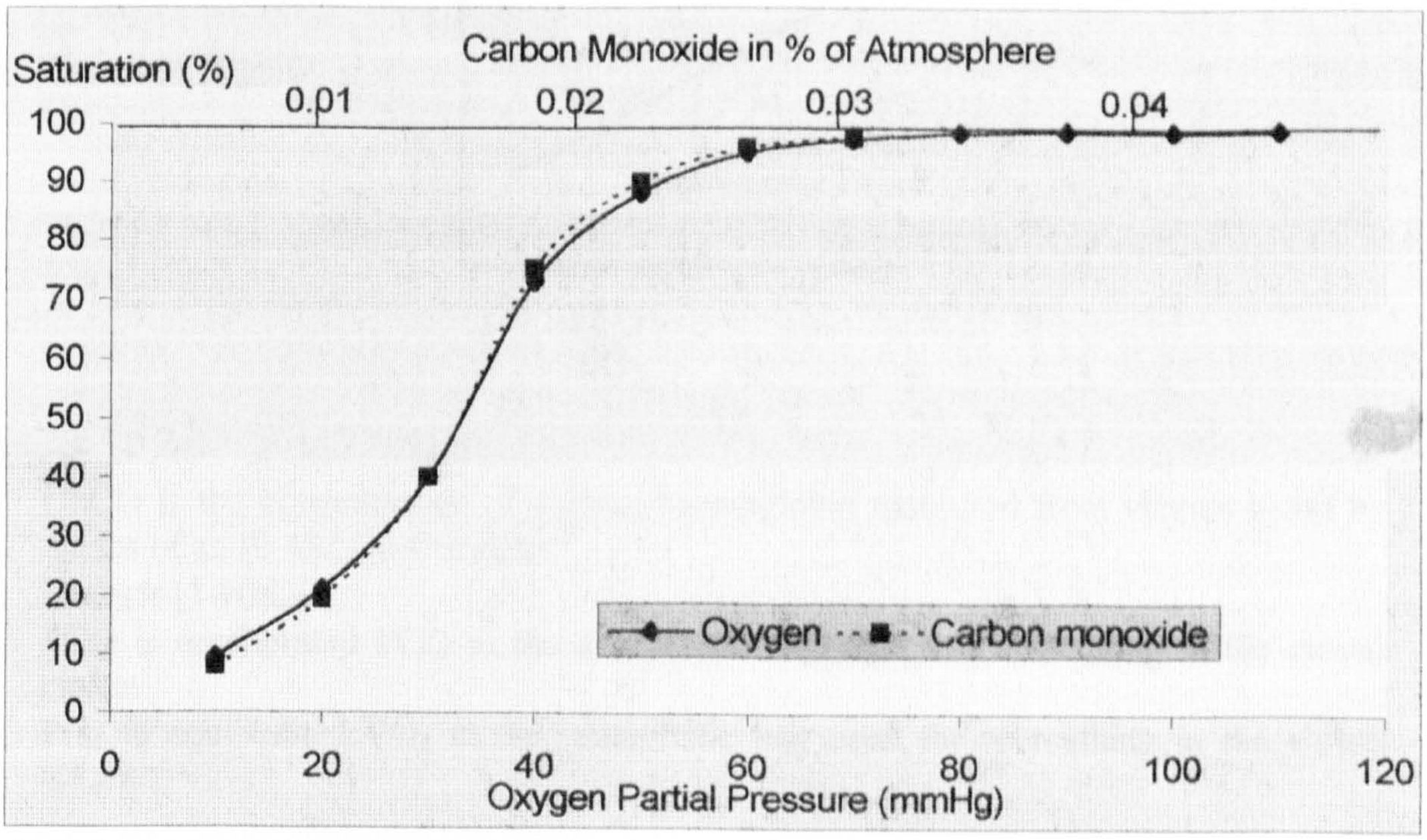
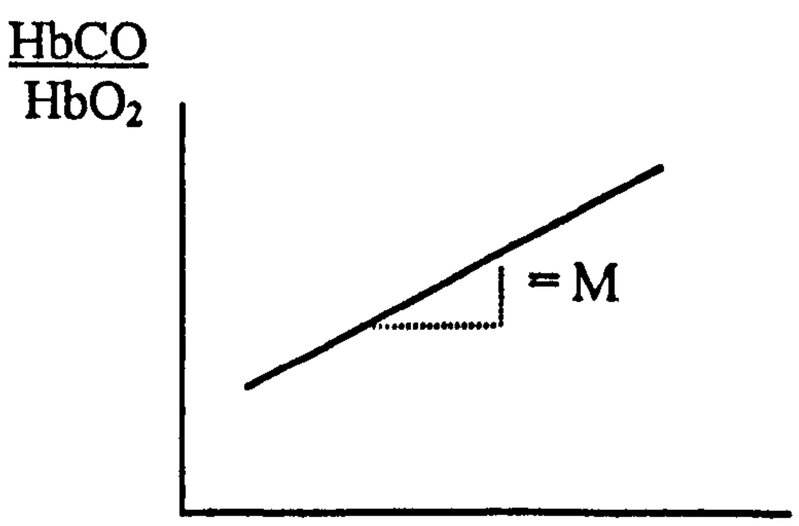


FIGURE G1, OXYHAEMOGLOBIN AND CARBOXYHAEMOGLOBIN DISSOCIATION CURVES. Adapted from Roughton (1954)

Haldane's constant is determined primarily by the ratio of the rates of association and dissociation of carbon monoxide with carboxyhaemoglobin and oxygen with oxyhaemoglobin. Although the rate of dissociation is relatively constant the rate of association is moderately labile and responsible for a fairly large variation in 'M' (Cotes, 1993). Factors which effect 'M' are environmental temperature, pH and the partial

pressure of carbon dioxide (Boothby, 1954; Cotes, 1993). Values as diverse as 223 to 333 (Dahlström, 1954) and 197 to 512 (Carlsten et al., 1953) have been calculated, however, values are more commonly in the region of 200 to 250 (Cardus et al., 1963; Peterson and Stewart, 1975; Cotes, 1993; Benignus et al., 1994).

In order to obtain an accurate measure of blood volume under the conditions employed in the present study, accurate measures of carboxyhaemoglobin were obtained by means a co-oximeter (IL482 Spectrophotometric Co-oximeter, Instrumentation Laboratory Ltd, Warrington, UK) for eleven blood samples. The blood samples were taken from subjects who had been rebreathing on the experimental apparatus for 15 min after between 0 and 75ml of carbon monoxide had been introduced to the closed circuit. Haldane's constant in this case was calculated thus:



$$\frac{PCO}{PO_2}$$

Where:

- HbCO is the concentration of carboxyhaemoglobin measured from venous blood by means of an IL 482 Co-Oximeter[24]
- HbO_2 is [1-HbCO]
- PCO is equilibrated PCO in the anaesthetic bag used for rebreathing in the closed circuit.
- PO_2 is equilibrated PO_2 in the anaesthetic bag used for rebreathing in the closed circuit.

[24] Assuming that [HbCO] has not changed from pulmonary to forearm vein.

The values obtained were:

	%		mmHg		Ratio	
1	HbCO	HbO_2	PCO	PO_2	A	B
2	0.7	99.3	0.02268	679.64	0.007049345	0.0000333
3	8.0	92	0.21924	637.38	0.086956522	0.000343971
4	1.16	99.84	0.00377	697.45	0.001602564	0.000005405
5	9.0	91.0	0.2488	686.14	0.098901099	0.000362637
6	0.9	99.1	0.01512	677.5	0.00908154	0.000022317
7	9.2	90.8	0.23436	586.6	0.101321586	0.00039523
8	2.7	97.3	0.0748	644.3	0.027749229	0.000116095
9	2.8	97.2	0.0748	644.3	0.028806584	0.000116095
10	4.4	95.6	0.11968	633.71	0.046025105	0.000188856
11	3.6	96.4	0.08976	668.11	0.037344398	0.000130444
12	3.8	96.2	0.08976	668.11	0.03950104	0.000130444

A Haldane's constant of 257 was derived as shown in Figure G2.

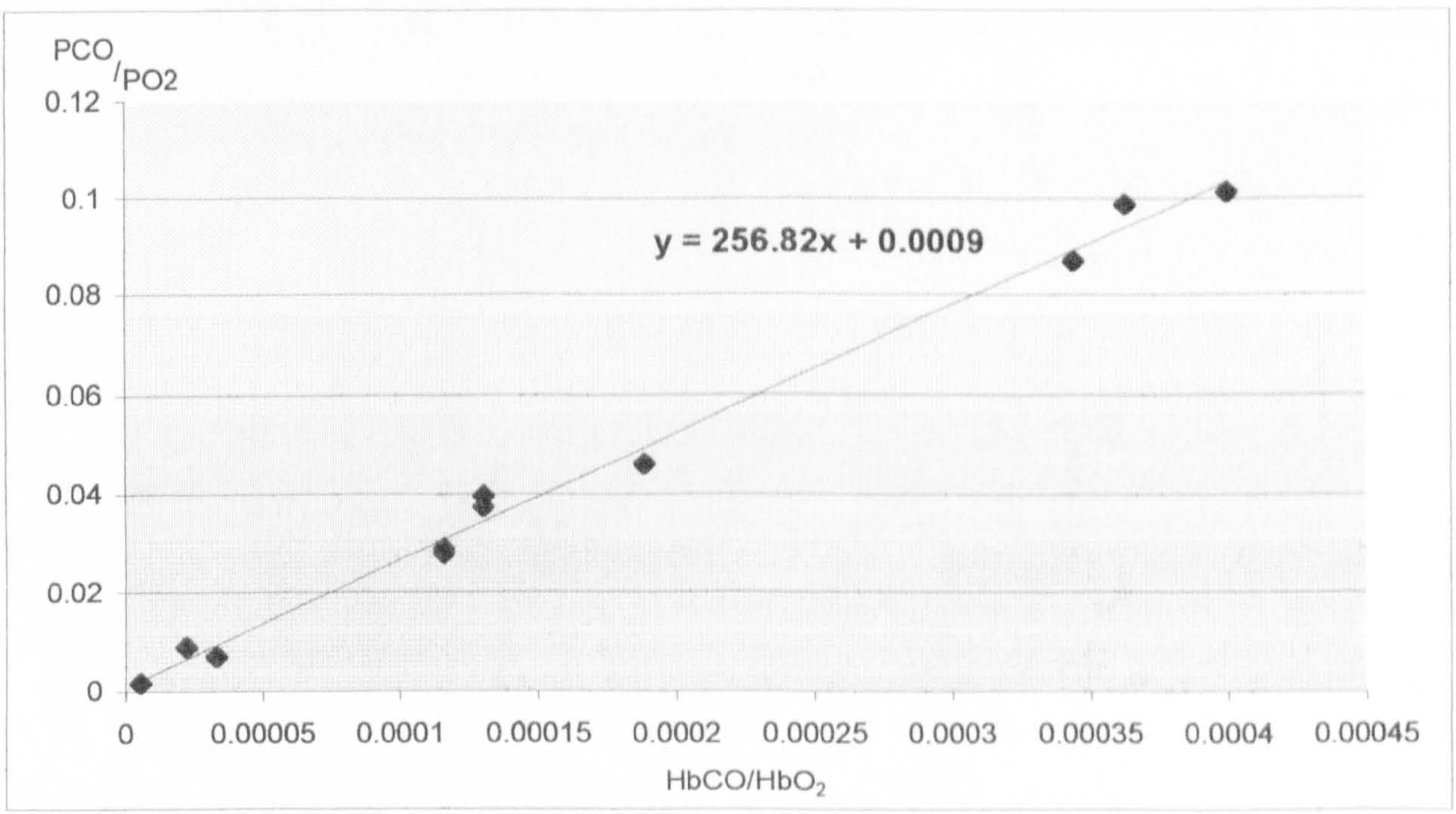


FIGURE G2, HALDANE'S AFFINITY RATIO (M)

Two measures were repeat measures for an assessment of reliability (rows 9 and 12). Elimination of these values in the plot retained the same slope as shown below (Figure G3).

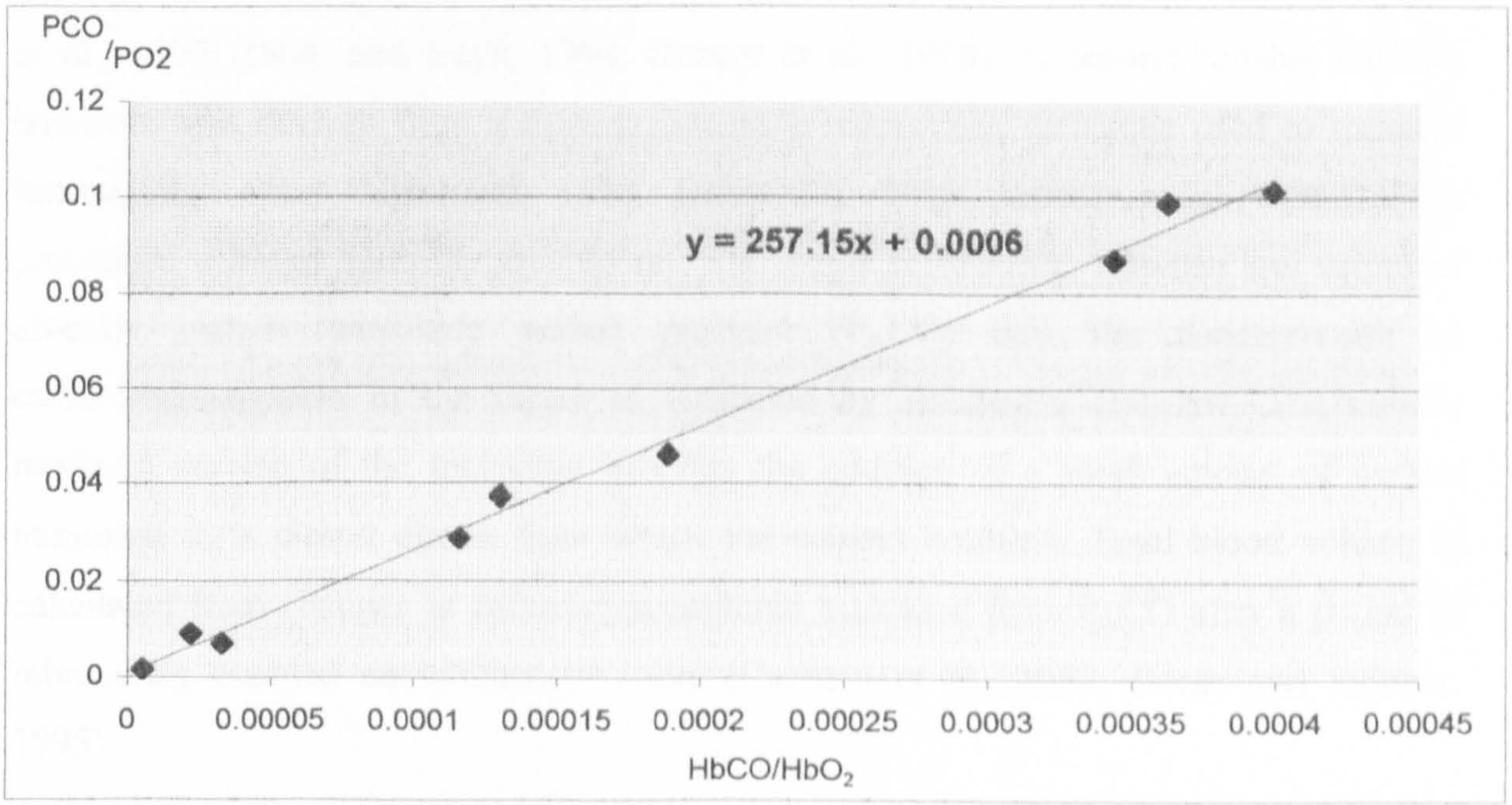


FIGURE G3, HALDANE'S AFFINITY RATIO (M)

METHODS OF MEASURING BLOOD VOLUME.

Traditionally blood volume in humans has been measured by means of the dye dilution technique particularly using Evans Blue dye (T-1824) (Best and Taylor, 1950; Greenleaf et al., 1977; Davy and Seals, 1994; Grover et al., 1998). A second reliable method, however, was derived from a carbon monoxide rebreathing technique used to measure haemoglobin mass (Sjöstrand, 1948; Dahlström, 1954; Cardus et al., 1963). The procedure is based upon the assumption of a simple relationship between low values of alveolar carbon monoxide partial pressure (P_ACO) and the concentration of carboxyhaemoglobin in the blood as predicted by Haldane's first law. The current modified version of the technique involves the addition of a small amount of carbon monoxide to a closed circuit from which the subject breathes. Total blood volume is calculated from changes in carboxyhaemoglobin estimated from P_ACO after a period of rebreathing enabled equilibrium to occur (Carlsten et al., 1953; Burge and Skinner, 1995).

In a comparison of blood volume as measured by the Evans Blue and carbon monoxide rebreathing methods (Myhre et al., 1968) the rebreathing values were within -1% and 4% of the Evans Blue values in 12 out of 16 subjects and between -7% and -13% for the remaining four. This degree of inaccuracy could be due to a lack of control resulting from the field conditions used i.e. at sea level in India, in a desert in summer and on a mountain at 3800m. In a more controlled comparison of techniques Thomsen and colleagues (1991) found that blood volumes derived from the carbon monoxide rebreathing method were significantly related to the plasma volumes measured using Evans Blue ($r = 0.91$) and blood volumes measured by radio isotope ($r = 0.92$). The mean blood volumes measured by the rebreathing and labelling methods were 4557 ± 959ml and 4527 ± 1008ml respectively. In a detailed study of the carbon monoxide technique Burge and Skinner (1995) examined the accuracy and reliability of the method using venisection. The coefficient of variation of the haemoglobin mass estimates was 0.8% for three weekly measurements of 7 subjects. A mean reduction in blood volume of 498 ml by means of venisection was measured to be 508 ml using the carbon monoxide rebreathing method ($n = 6$).

VALIDITY ASSESSMENT OF NECK CUPS FOR STIMULATION OF THE CAROTID SINUS

Plastic neck cups and associated apparatus for stimulating the carotid sinus were developed as outlined in chapter 3. This appendix summarises the preliminary work undertaken to validate the apparatus and technique eventually used to measure carotid sinus baroreceptor function.

Carotid Sinus Stimulation Without Automated 'R' Wave Coupling Activation.

Initially manual activation was used to examine the responses derived from the use of cups compared to a lead collar (Eckberg et al., 1975) (Fig I.1). The apparatus consisted of a vacuum source, tubing, a 30mm diameter flow control tap and a mercury manometer to measure pressure applied to the neck (Fig I2).

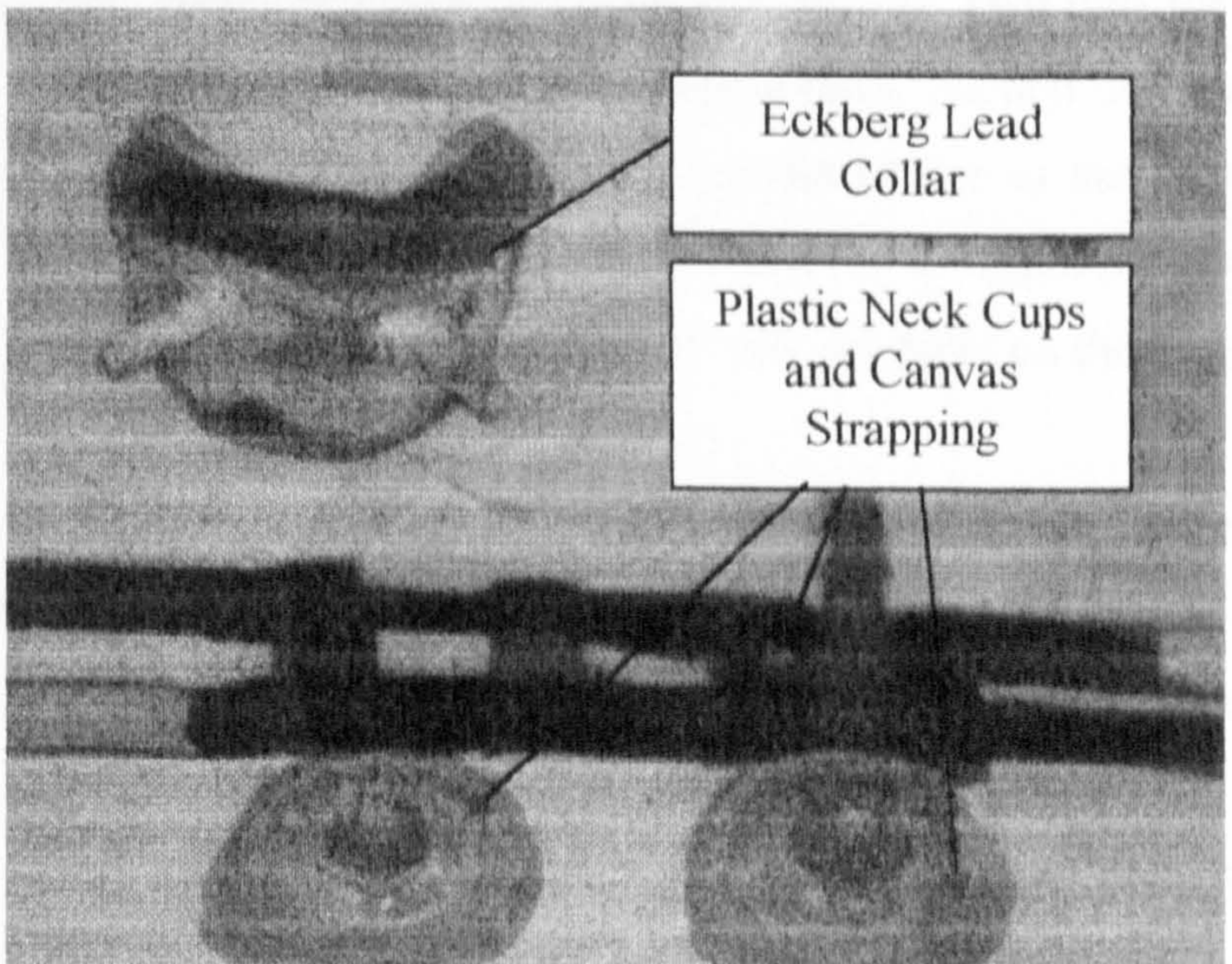


FIGURE I.1, CAROTID SINUS STIMULATION CUPS AND 'ECKBERG' LEAD COLLAR.

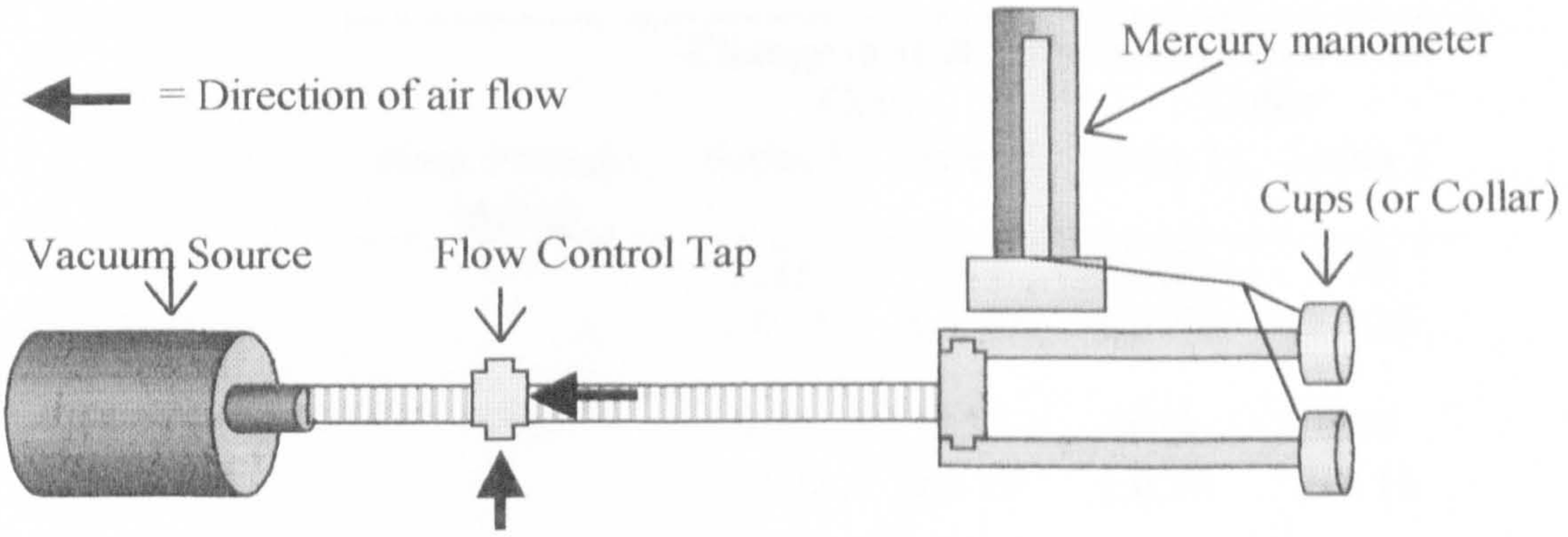


FIGURE 12, PRELIMINARY CAROTID SINUS STIMULATION APPARATUS

COMPARISON OF ELECTROCARDIOGRAM R-R RESPONSES DERIVED FROM USE OF NECK CUPS AND ECKBERG COLLAR

Five subjects (4 female and 1 male) were exposed to trains of 8 to 12 neck pressures using the cups and collar on different occasions (Fig I.3). Two runs for each device were undertaken at the same time of day on subsequent days. Suction was applied manually by rapidly turning a flow valve connecting the suction source to the cups/collar, providing negative pressure to the neck of a mean duration of 0.5 s. Applications were made during held expiration and were not timed to coincide with any point on the QRS cycle.

Results. A single factor ANOVA combined with Tukey's post hoc analysis of means revealed the mean responses produced using cups (series 1) and collar (series 1) at –40 mmHg were significantly less than the mean response produced using cups (series 2) at –50 mmHg (Table I.1). The mean collar response (series 1) at –40 mmHg was also significantly less than the mean responses produced using cups (series 1 and 2) at –60 mmHg. No other significant differences were found between series means for a given device.

	Change in R-R Interval (s) Mean ± SD			
	Cups		Collar	
Neck Pressure, mmHg	Series 1	Series 2	Series 1	Series 2
-40	0.21 ± 0.11	0.24 ± 0.12	0.19 ± 0.12	0.22 ± 0.15
-50	0.26 ± 0.13	0.31 ± 0.16	0.22 ± 0.14	0.22 ± 0.16
-60	0.30 ± 0.16	0.30 ± 0.17	0.28 ± 0.17	0.26 ± 0.20

TABLE I.1. MEAN R-R INTERVAL RESPONSES TO NECK SUCTION USING A NECK COLLAR AND NECK CUPS. Underscore denotes significant difference to Cups –50 series 2. Double Underscore denotes significantly different to Collar –40 series 1

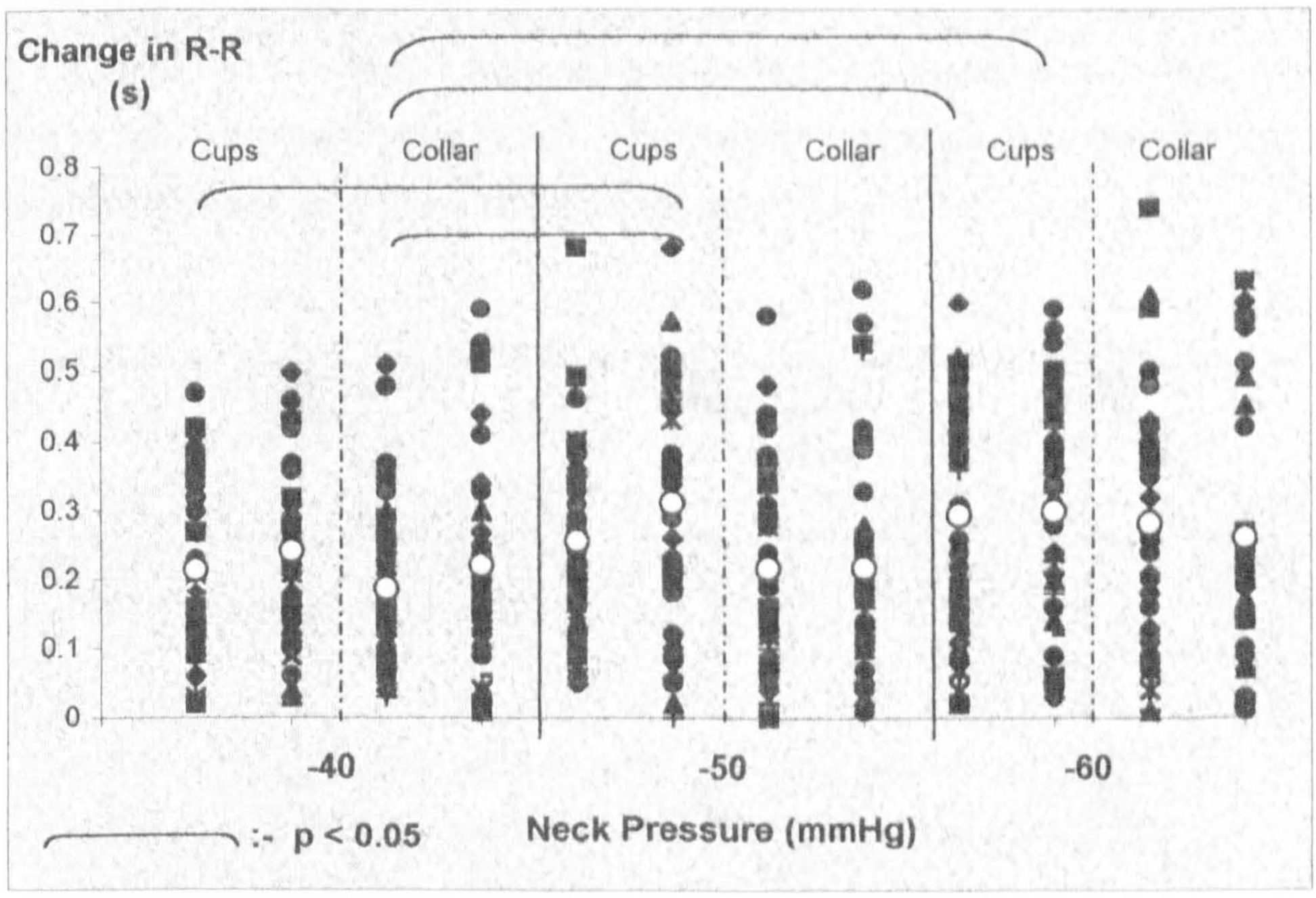


FIGURE I.3. R-R INTERVAL RESPONSES TO NECK SUCTION USING A LEAD COLLAR OR PLASTIC MOLDED CUPS. The R-R interval responses of 5 subjects to suction between –40 and –60 mmHg are shown in green. Each series of pressures was applied twice for each device at each pressure. The Empty circles show the mean for each pressure/device/series combination.

Examination of the standard deviations of the runs showed that considerable variance existed in some cases indicating that within subject reliability could not be assured using this method (Table I3). For a given device, however, the means of each series were not significantly different from each other thus indicating that the use of a mean of a large number of responses achieves acceptable reliability. Furthermore, the mean responses using the cups were at all times as great or greater than those derived from use of the collar, indicating that the use of the neck cups was valid in this case (see Appendix O for full validation study).

COMPARISON OF ECKBERG COLLAR AND CUPS RESPONSES RELATIVE TO THE ELECTROCARDIOGRAM R WAVE.

Stimuli were applied to the neck of one subject wearing neck cups on one occasion and whilst wearing an Eckberg collar on another, on separate days at the same time of day (Figs I.4 and I.5). The stimuli were applied during held expiration and were random relative to the electrocardiogram R wave. The subject was exposed to between five and eight applications at four different pressures for each device.

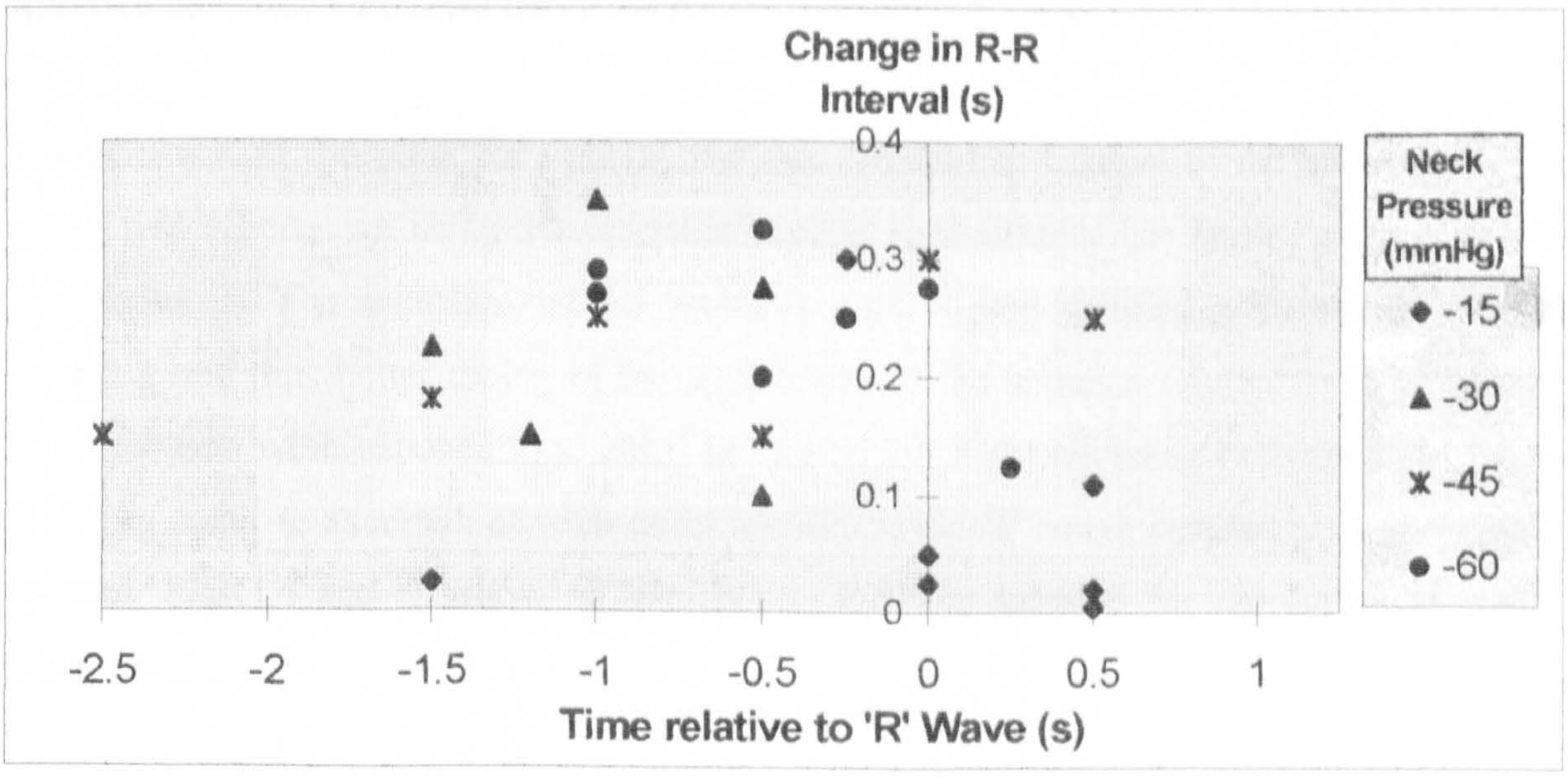


FIGURE I.4 SHOW MEAN CHANGES IN R-R INTERVAL RESULTANT FROM NECK SUCTION (USING A NECK CUPS) RELATIVE TO THE ELECTROCARDIOGRAM 'R' WAVE. The neck pressure applications were applied randomly but plotted relative to the nearest 'R' wave. Four pressures were applied (-15, -30, -45 and –60 mmHg) between 5 and 8 times.

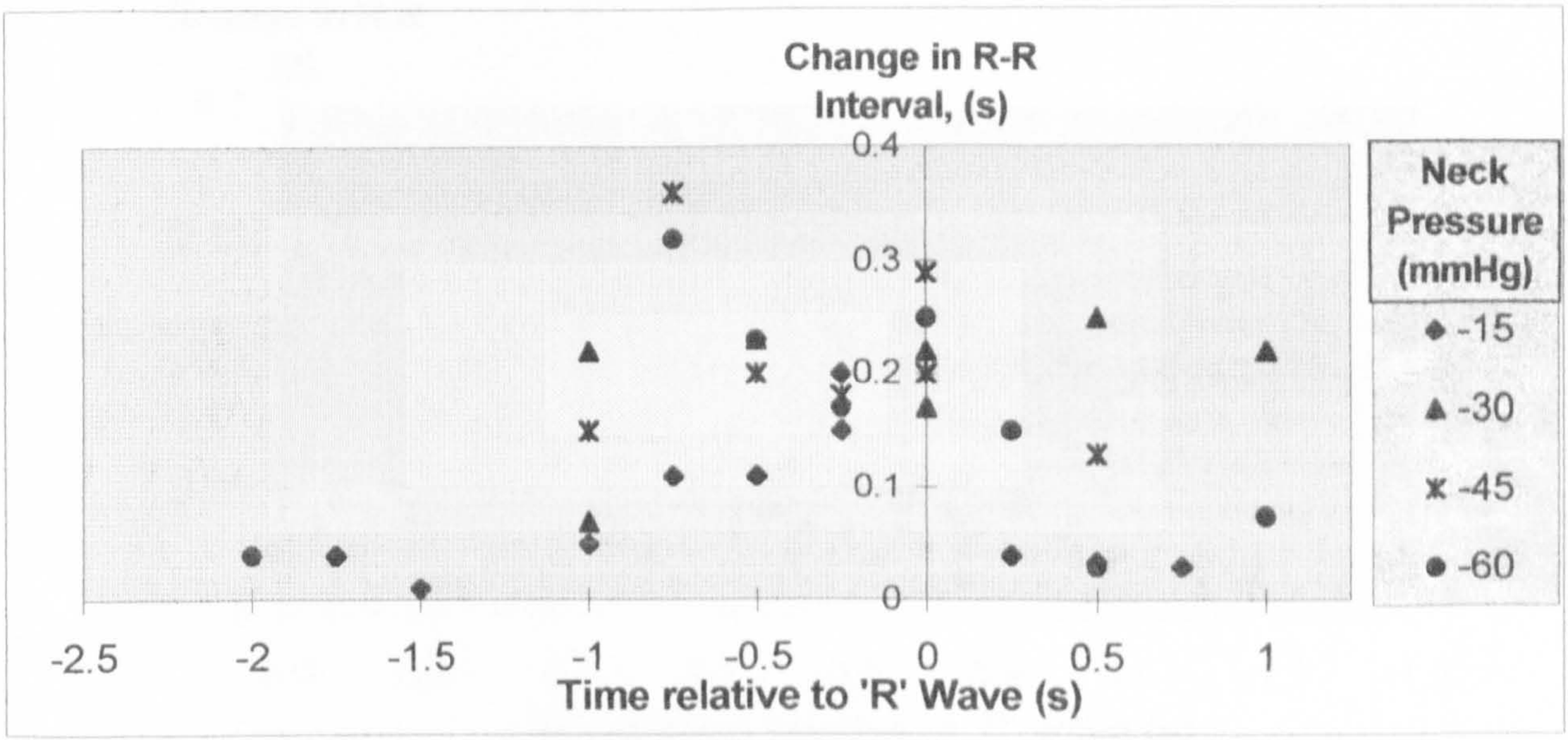


FIGURE I.5 SHOW MEAN CHANGES IN R-R INTERVAL RESULTANT FROM NECK SUCTION (USING A LEAD COLLAR) RELATIVE TO THE ELECTROCARDIOGRAM 'R' WAVE. The neck pressure applications were applied randomly but plotted relative to the nearest 'R' wave. Four pressures were applied (-15, -30, -45 and –60 mmHg) between 5 and 8 times.

The results were in agreement with Eckberg's findings that an optimal point relative to the 'R' wave exists for the elicitation of a response from the carotid baroreceptors. The point was in the region of 0.5 – 1.0 seconds before the 'R' wave for the neck cups and approximately 0.75 s before the 'R' wave for the Eckberg collar.

Confirmation of the point for optimal stimulus application relative to the anticipated 'P' wave was ascertained using the complete carotid sinus stimulation apparatus as outlined in chapter 3. The inclusion of the stimulus control unit enabled accurate 'R' wave coupling and thus better timing of the application of the stimulus relative to the P wave. Two subjects were exposed to a series of carotid sinus stimuli using both neck cups and Eckberg collar to ascertain at what point relative to the 'P' wave optimal responses were elicited. Figs I.6 and I.7 show all data points for both subjects for the cups and collar respectively.

The optimal range for stimulation for each device in this instance was between 0.7 and 0.85 s before the anticipated 'P' wave.

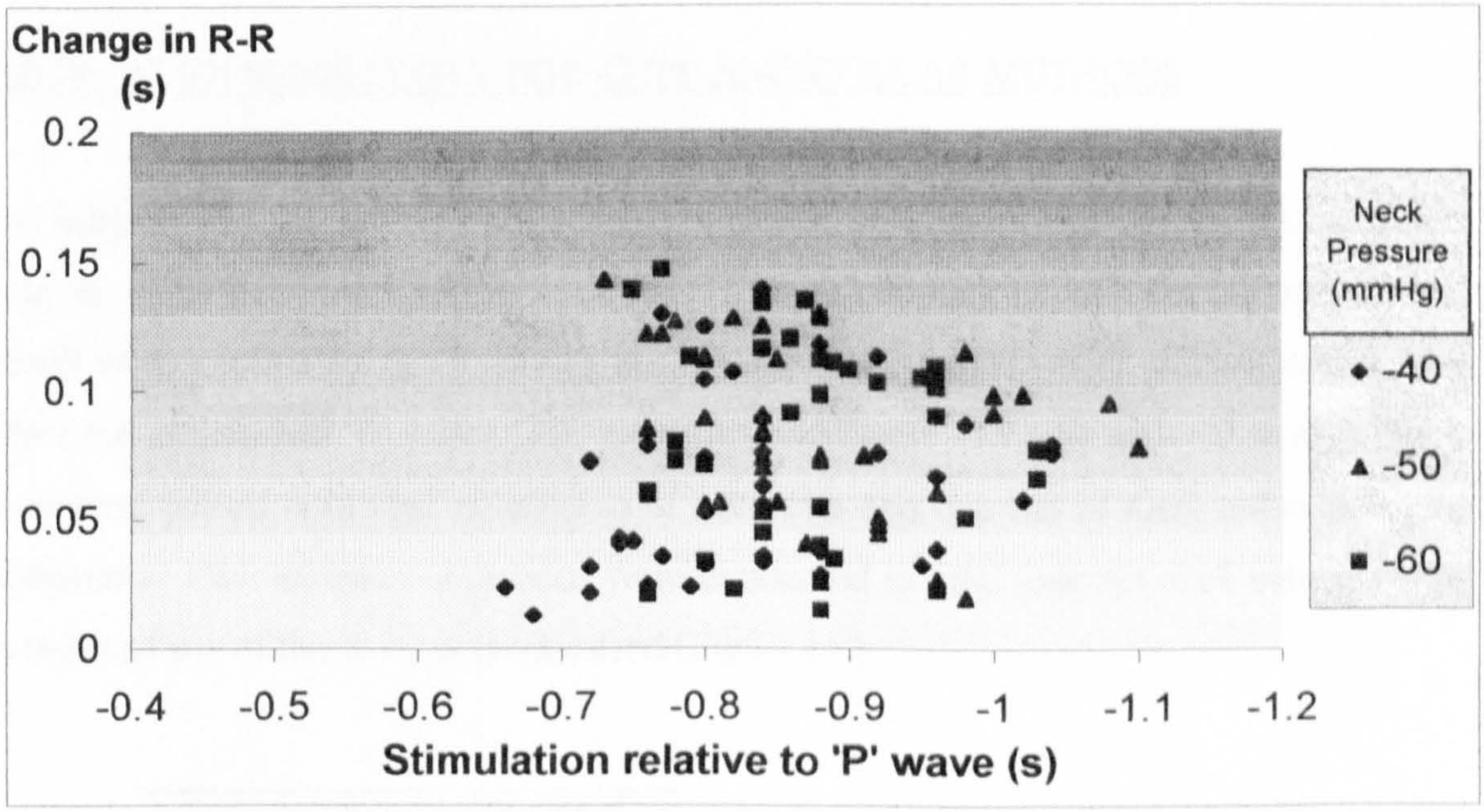
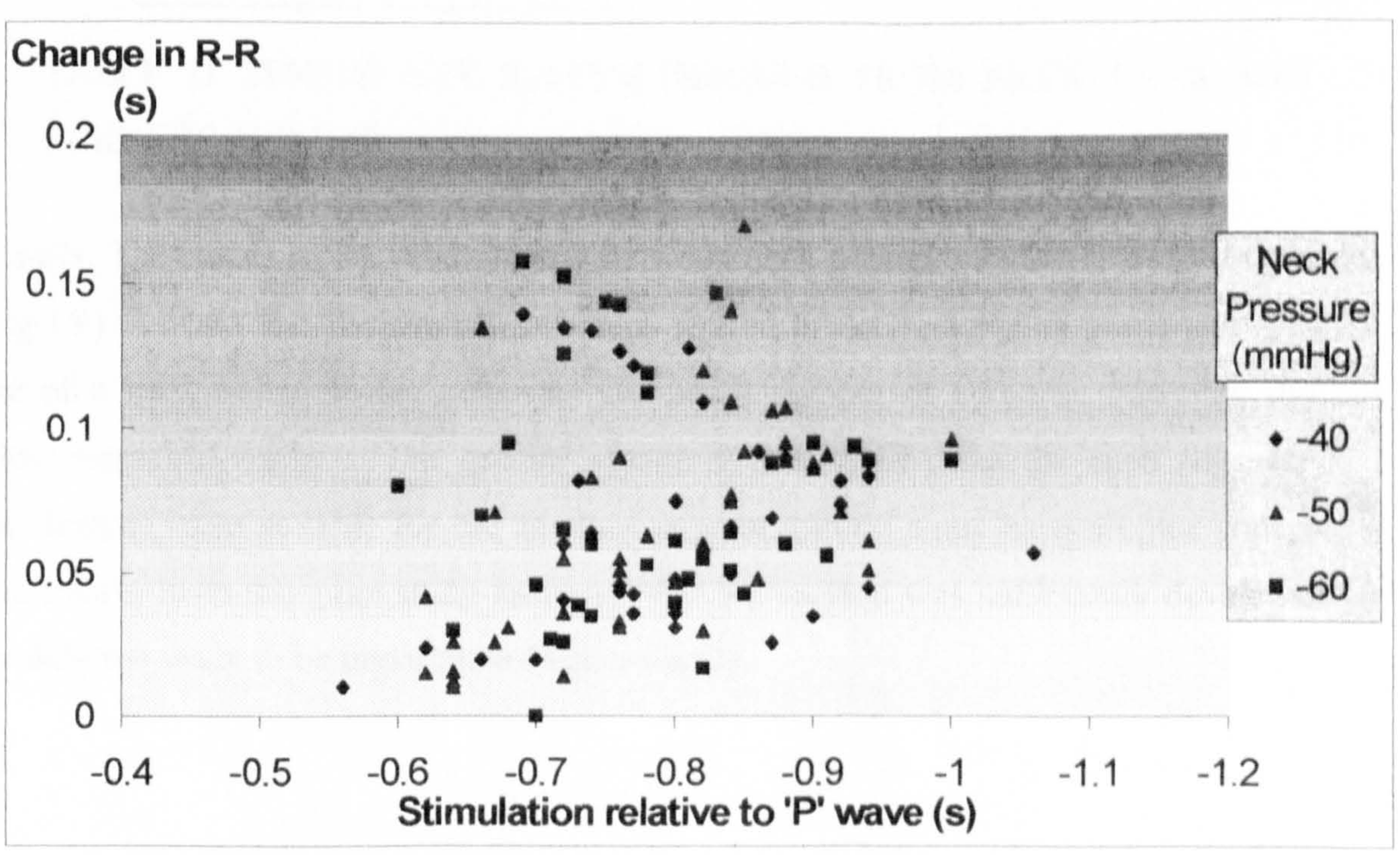


FIGURE I.7 (ABOVE – CUPS) AND I.8 (BELOW – COLLAR) R-R INTERVAL RESPONSES TO NECK SUCTION TIMED RELATIVE TO THE ELECTROCARDIOGRAM 'P' WAVE. Series of neck pressures were applied to the necks of 2 subjects at specific times prior to the 'P' wave of the QRS cycle. The greatest response was derived from stimuli in the region of 0.7 to 0.85 s before the 'P' wave.



BAROREFLEX SENSITIVITY FOR CUPS AND COLLAR METHODS.

Five subjects had the carotid baroreceptor response to trains of neck pressures measured using the same equipment as that used for 'P' wave coupling experiment outlined above. Stimuli were applied for 0.6 s, during normal expiration i.e. not held and initiated 0.75 s before the anticipated 'P' wave. The pressures used were -15, -30 and -40 mmHg. Each assessment period consisted of one run of neck cup and one run of neck collar pressure applications. Five assessment periods were conducted in total (one for each subject) with the order of use of the devices randomised (Figure I.9).

	Slope, ms.mmHg^{-1}	
Subject	Cups	Collar
1	40.53	23.68
2	41.84	12.10
3	20.79	7.89
4	18.95	1.18
5	15.53	-3.16

TABLE I1 SENSITIVITY SLOPES DERIVED FROM NECK CUPS AND ECKBERG COLLAR

Results. The slopes of the relationships between neck pressure and R-R interval response (Fig I.9) indicate that the use of neck cups tended to derived greater responses than the use of a neck collar in this instance. The small number of subjects, however, did not allow statistical analysis. The greater sensitivity measured using the cups suggests that the devices were suitable for the measurement of carotid sinus baroreceptor sensitivity. The results from this pilot study indicated that the method was sufficiently developed for a validation study to be undertaken (Appendix O).

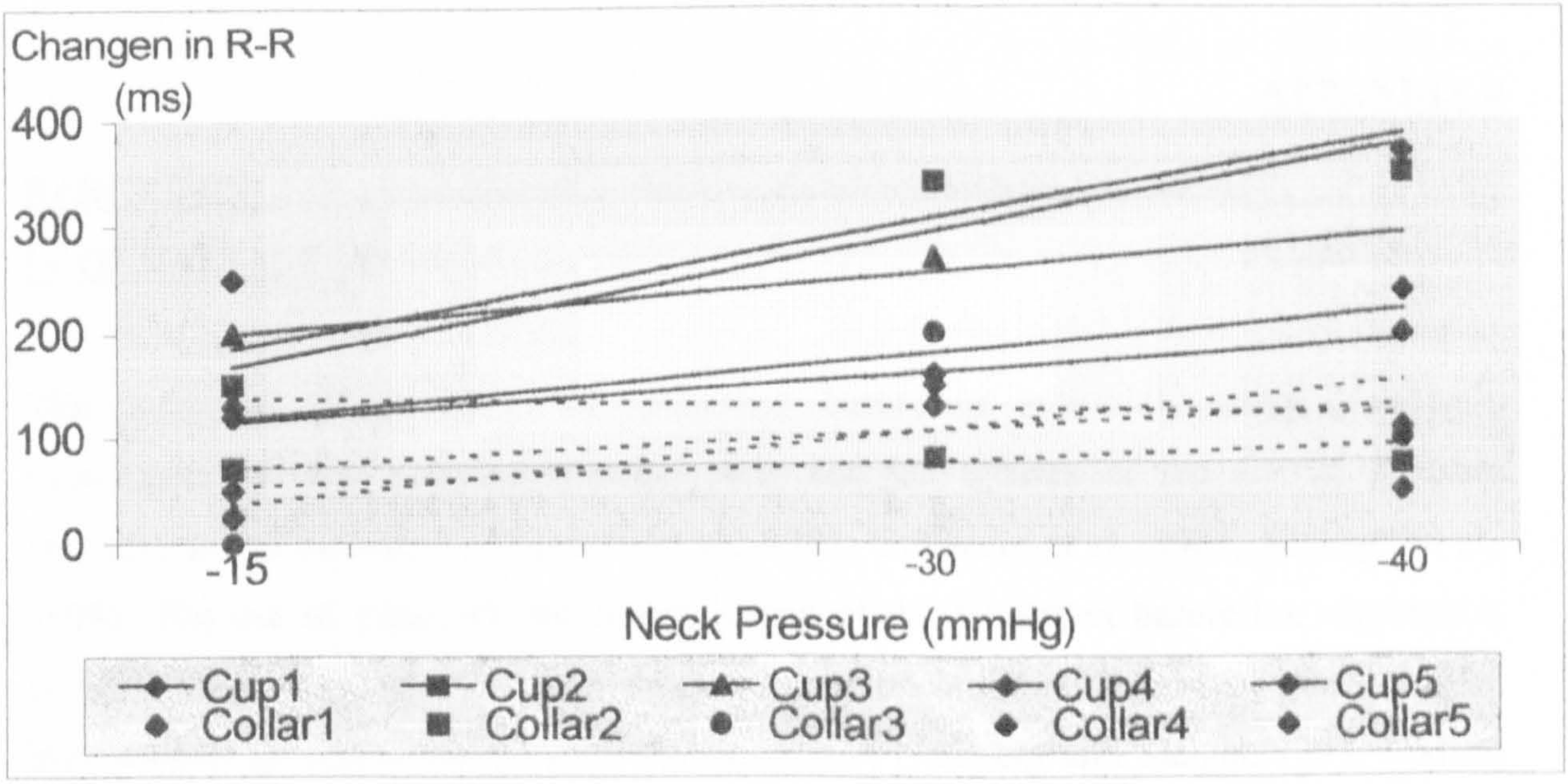


FIGURE I.9. CAROTID BARORECEPTOR SENSITIVITY SLOPES DERIVED FROM THE USE OF NECK CUPS AND NECK COLLAR. The slopes of the relationships between neck pressure and change in R-R interval indicate that the use of neck cups (solid lines) derived greater responses than the use of a neck collar (dashed lines).

SUMMARY.

- The variation of R-R interval responses to negative pressures of 0.6 s duration applied to the neck when not timed relative to electrocardiogram 'P' wave, was sufficiently large to preclude the possibility of intra-subject comparison of single responses for neck cups or Eckberg collar.
- The mean responses of two series of 8 to 12 stimuli at each (three) level of neck pressure were not significantly different between devices, thus indicating adequate reliability when a large number of responses are considered.
- Application of neck pressure relative to the electrocardiogram 'R' wave indicates that an optimal point of application in the region of 0.7 to 0.85s prior to the anticipated 'P' wave exists, irrespective of method used.
- The application of negative pressure to the neck of 0.6 s duration, 0.75 s prior to the anticipated 'P' wave, during expiration using plastic neck cups produced greater responses than that measured using a lead collar. This was highlighted by the steeper slopes of the relationships between R-R interval and applied neck pressure when 4 series of neck pressures were used.

APPENDIX J

BARORECEPTOR SENSITIVITY INDEX CALCULATION BY MEANS OF PHASE IV OF VALSALVA'S MANOEUVRE

The derivation of an index of integrated baroreflex sensitivity using Valsalva's manoeuvre has been conducted using early and late phases of the arterial pressure response to the manoeuvre (Palmero et al., 1981; Goldstein et al., 1982; Schlegel et al., 1998). The use of phase IV for investigations of the integrated baroreflex response is probably more appropriate than other phases because of the involvement of all baroreceptor groups at this point in the manoeuvre (Eckberg and Sleight, 1992; Ludwig et al., 1998). Furthermore, baroreflex slopes derived from phase IV have been found to correlate closely with slopes derived from bolus pressor injections (Palmero et al., 1981; Goldstein et al., 1982). There has, however, been some disagreement as to which R-R interval to associate with a given systolic pressure wave to calculate baroreflex sensitivity (Palmero et al., 1981). The use of the interval immediately succeeding the pulse wave or the interval after that have been adopted according to the physiological response time is assumed. That is, if the time for the reflex response to a given arterial pressure change assumed to be greater than 1 s and R-R intervals are approximately 0.9 s, then the R-R interval after the interval succeeding a stimulus is used. In order to address this issue a preliminary investigation of the relationships between systolic pressure and succeeding R-R intervals of phase IV of Valsalva's manoeuvre was undertaken to ascertain how much temporal lag should be assumed for the physiological response time of the integrated baroreflex.

METHOD. The arterial responses to Valsalva's manoeuvre of six subjects were recorded during the baseline measurements for the first parabolic flight campaign. The in-flight equipment assembly comprising of Portapres, TEAC data recorder and electrocardiogram was used for measurement (see Appendix L). Responses to three Valsalva's manoeuvres conducted whilst seated and three whilst at 6° head-down tilt were recorded for each subject. The R – R intervals associated with systolic arterial pressures during phase IV of the manoeuvre were used for BRSI calculation. Regression lines were plotted for these variables using the R – R interval immediately following the systolic peak ('0' offset), the second interval after ('+1' offset) and the third interval after ('+2' offset) the systolic

peak. Pearson correlation coefficients were calculated for the relationship of R-R interval to systolic pressure for each offset for each Valsalva response.

RESULTS. Table I.1 lists the correlation coefficients for all manoeuvres according to subject and offset. A significantly stronger mean correlation ($p < 0.05$) was found between systolic pressure and the first R-R interval ($r = 0.85 \pm .09$ [zero-offset]) than for the second ($r = 0.66 \pm 0.18$ [+1 offset]) or third interval ($r = 0.27 \pm 0.34$ [+2 offset]).

R-R Offset	Subject's Correlation Coefficients						Grand Mean ± SE
	SE	JM	LJ	RW	IT	SS	
'0'							
Mean	0.94	0.81	0.72	0.79	0.91	0.93	**0.86**
± SD	0.08	0.09	0.11	0.20		0.06	**0.10**
'1'							
Mean	0.86	0.55	0.63	0.45	0.91	0.59	**0.66**
± SD	0.13	0.24	0.28	0.16		0.27	**0.18**
'2'							
Mean	0.79	0.13	0.35	-0.08	0.49	-0.08	**0.27**
± SD	0.17	0.47	0.49	0.79		0.93	**0.34**

TABLE I.1 PEARSON CORRELATION COEFFICIENTS FOR THE RELATIONSHIPS BETWEEN SYSTOLIC ARTERIAL PRESSURE AND R-R INTERVAL (n = 6). Only one set of data was obtained from subject IT.

DISCUSSION. The stronger relationship between arterial pressure change and change in R-R interval immediately succeeding the pressure wave supports the use of the first R-R interval after a given systolic peak. Eckberg during the development of the lead collar for carotid sinus stimulation reported that if the stimulus (negative pressure about the neck) was applied early in a cardiac cycle the R-R interval for that specific cycle was prolonged (Eckberg et al., 1975). This finding was also noted during the development of neck cups for the same purpose during this study. Eckberg went on to quantify the arterial baroreflex response time to be in the region of 0.24 sec. Although the response to phase IV of the Valsalva's manoeuvre does not purely derive from the arterial baroreceptors these receptor groups play the dominant role in response to a rapid rise in arterial pressure (Eckberg and Sleight, 1992). Pickering and Davies (1973) examined cardiac slowing resulting from elevated arterial pressure produced by a bolus injection of phenylephrine and found that responses occurred from 0.475 s after the initial rise in blood pressure. It would appear, therefore, that the response of the integrated baroreflex to a moderately rapid change in arterial pressure occur in less than 0.5 s.

The mean R - R interval at the start of phase IV for the subjects examined in this study was 490 ± 50 ms increasing to 800 ± 120 ms at the point of maximum systolic pressure. Consequently, it would appear that the response delay to a systolic pulse at the start of the phase IV pressure elevation would result in the initiation of cardiac slowing before the next R wave. As the R-R intervals lengthened so the start of the response to each preceding systolic pressure would occur relatively earlier in the succeeding interval, but the slowing would always commence in that interval and not the next. The significantly stronger correlation coefficients derived from the '0' offset calculations in this study support the use of the first R-R interval after each systolic pressure for the calculation of integrated baroreflex sensitivity.

APPENDIX K

PARABOLIC FLIGHT WEEK SUMMARY

Day	Activities	Comments
Sunday	Travel to Bordeaux	
Monday	Health & Safety brief + aircraft brief.	All to attend
Tuesday	Flight 1 (3 pax)	3 as nominated
Wednesday	Flight 2 (3 pax)	3 as nominated
Thursday	Flight 3 (3 pax)	3 as nominated
Friday	Back-up flight day and or travel back to UK	Probable return day
Saturday	Travel back to UK	

PARA FLIGHT DAY - In Flight Schedule

1. 30 parabolas of:

- 20 s +1.8G, 30 s '0'G, 20 s +1.8 G, 120 s +1G.
- 15 parabolas, 5 minute break, 15 parabolas.
- ½ hour flight to and from parabola flight path area.

2. Flight to Para area.

- Valsalva rehearsals in situ.

3.

Parabola	**Action**
1, 2	Familiarisation
3, 4, 5	1 rehearsal/subject + change over between all subjects.
6, 7, 8	Subj 1 Valsalvas
9, 10, 11	Subj 2 Valsalvas
12, 13, 14	Subj 3 Valsalvas
15	Spare
Break for 5 mins	**Equipment check, battery change over if needed.**
16, 17	Subj 1 Valsalvas
18, 19	Subj 2 Valsalvas
20, 21	Subj 3 Valsalvas
22, 23, 24, 25	Re-runs as needed
26, 27	Spare
28, 29, 30	'Odd G' parabolas.

PARA-FLIGHT DAY – Post Flight Admin

ACTION	LOCATION	DURATION
'Landing + 0 min'		
1. Equipment 'unstowed' from a/c	A300	10 min
• Check all equipment removed from a/c		5 min
		15 min
(Move to Office 20 minutes)		
'Landing + 35 min'		
2. Baseline Valsalvas (inc Cals)	Office/Lab:	
Wash-up !?		10 min
Subj 1: - 5 x Val Seated, 5 x Val Horizontal or (HDT ?)		20 min
- Real time 'T' to 4 channel recorder.		-
- Check playback from TEAC/Porta set-up (via TEAC main unit) to 4 chan is OK.		10 min
Subj 2: - 5 x Val Seated, 5 x Val Horizontal or (HDT ?)		20 min
- Real time 'T' to 4 channel recorder.		-
- Check playback from TEAC/Porta set-up (via TEAC main unit) to 4 chan is OK.		10 min
Subj 3: - 5 x Val Seated, 5 x Val Horizontal or (HDT ?)		20 min
- Real time 'T' to 4 channel recorder.		-
- Check playback from TEAC/Porta set-up (via TEAC main unit) to 4 chan is OK.		10 min
	Total	**100 min**
'Landing + 135 min'		
3. Pack-up	Office	
• Turn off and secure equipment.		15 min
4. De-brief		10 min
'Landing + 160 min'		
- PUFO		
5. Evetts only - Play back tapes and record to 4 chan		**1 hour ?**

FLIGHT DAY SUBJECT RECORD SHEET

Name:_____Date:_____Time:_____

Flight: _____ Time Stugeron taken: _____

Last meal taken ?_____

1. Pre Baseline:

BP:_____ HRSit:_____

Seated	**HDT**
00.00	00.00
02.10	02.10
04.20	04.20

2. Post Baseline:

Time: _____ BP:_____ HRSit:_____

Seated	**HDT**
00.00	00.00
02.10	02.10
04.20	04.20

Comments:

Debrief.....

Subject Debrief - Post Parabolic Flight.

Name: _____ **Date:**_____ **Flight:**____

General Flt details:

- Weather conditions:_____

  ...effect on Flt:_____

- Number of Parabolas:_____ Duration of Flt:_____

Subject Wellness:

- Nausea:

  Vomiting ($^{10}/_{10}$)_____ Degree of nausea ($^{7}/_{10}$)_____

- Other symptoms:

  Dizziness _____
  Light headedness _____
  Tiredness _____
  Disorientation _____
  Other: _____
  _____

Degree of incapacitation:

- General impairment of Valsalva manoeuvre performance:

Completely impaired.	( )
Almost completely impaired	( )
Partially impaired	( )
Very slightly impaired	( )
Normal	( )

- Which periods/ how long did the impairment occur:

_____

_____

- Number of Valsalva Manoeuvres attempted: _____

- Number of successful manoeuvres: _____

Bordeaux Equipment List

Flight Equipment

1) **Portapres:-**
   - Main Unit
   - Pressure unit
   - x Battery blocks
   - Battery Re-charger
   - + lead
   - Front end
   - + lead
   - finger cuffs
2) **TEAC:-**
   - Monitor
   - Recorder
   - Lead Connection
   - Tapes
   - Microphone
3) **Timer Unit**
   - + lead
4) **Transducer**
5) **Transducer Amp**
   - + lead
   - + 'T' piece
6) **LED**
   - + lead
7) LED Battery
8) **ECG Amp**
   - + lead
9) 4 x 3 Lead assembly
10) 4 x Mouthpiece assembly
11) Straps + buckles

Ground Equipment

12) **4 Channel Recorder (Ser: 5045-48)**
    - + power lead
    - + 4 leads
    - + 4 rolls of thermal paper
13) **TEAC playback system**
    - + power lead
14) ECG monitor (Ser: 95380517)
    - + power lead
    - + 3 lead ECG
15) Tools (3 x screwdriver, pliers)
16) Millivolt box.

Other

17) Strerilisation fluid (for mouthpieces)
18) Tub (for sterilisation)
19) 4 x spare manometer tubing
20) 2 x Transpore tape
21) 100 x Red dot **electrodes**
22) Skin scourer
23) Alcohol swabs
24) Shaving kit
25) Spare velcro tape
26) 2 x packets of **Stugeron** (24tabs)
27) Video camera
    - + batteries
    - + 4 tapes

Batteries:

28) 4 x Portapres batts
29) Portapres NiCd Recharger
30) 60 x 9V Alkaline Battery

NON-INVASIVE ARTERIAL PRESSURE MEASUREMENT SYSTEMS AND PARABOLIC FLIGHT EQUIPMENT

FINAPRES

In the last three decades the use of non-invasive arterial pressure measurement has grown from a rare occurrence to one that is common to many human cardiovascular research studies. The first moderately accurate, mass produced device was the Finger Arterial Blood Pressure System (Finapres) produced by TNO Biomedical Instrumentation in the Netherlands (Imholz et al., 1988). The system is based on the volume clamp method of Penàz using an infrared photoplethysmograph and electropneumatic servo (Penàz, 1973). A small cuff is placed around the finger and inflated to a pressure equal to that of the artery beneath, effectively reducing transmural pressure across the artery wall to zero. The volume of blood in the artery is monitored by means of the photoplethysmograph and cuff pressure is controlled using the fast-acting electropneumatic servo system so as to maintain the blood content of the section of finger constant thus keeping the transmural pressure at zero. At zero transmural pressure the cuff pressure is equivalent to arterial pressure thus enabling intra-arterial pressure to be measured non-invasively. The volume clamp set point is regularly adjusted (self calibrated) to ensure transmural pressure remains constant over time.

The Finapres system has been shown to closely reproduce intra-arterial pressure measurements, however, studies have shown a tendency for it to under-estimate brachial artery measurements by between 1 and 9 mmHg (Molhoek et al., 1984; Van Egmond et al., 1985; Imholz et al., 1988). Imholz and co-workers (1988) examined the effectiveness of Finapres at measuring the arterial pressure of hypertensive subjects (measured at the brachial artery) during the Valsalva manoeuvre (Imholz et al., 1988). Their findings showed that the Finapres temporal reproduction of the arterial pressure response to the manoeuvre was accurate and reliable, however, the device tended to overestimate systolic pressure during phase II of the manoeuvre by about 6 mmHg[25] and underestimate mean, diastolic and systolic pressure during phase IV (post expiratory effort) by 4, 5 and 7 mmHg respectively. The authors comment that although the device may show more pronounced pulse pressures and dicrotic notches in the finger during rapid changes in arterial pressure, the reliability of measurement was sufficiently good to offer an

[25] Little difference in mean and diastolic values to intrabrachial measures

alternative to intra-arterial pressure measurement for most cardiovascular research purposes.

Imholz and colleagues (1990) and Jellema and associates (1996) during examination of Finapres measurement compared to intrabrachial measures found that baseline (supine at rest) arterial pressures differed little from intra-arterial. During manoeuvres which produced similar responses to phase IV of Valsalva's manoeuvre (blood pressure response 20 to 30 s after standing up – Imholz and colleagues (1990) and rapid reclining from 70° head-up tilt to horizontal – Jellema and co-workers (1996)), however, each study observed greater Finapres systolic measures than intra-arterial (+11 mmHg Imholz and colleagues (1990), +8 mmHg Jellema and associates (1960)). The apparent lack of support for the phase IV Valsalva's manoeuvre lower Finapres measurements derived by Imholz et al (1988) may be due to the subject groups used. Pulse pressures measured by the Penàz technique appear to show an inverse relationship with age, probably as a result of increased artherosclerosis in older subjects. The hypertensive subjects (mean age 50 yr) used by Imholz and colleagues in 1988 would almost certainly have had higher levels of artherosclerosis than younger or normotensive subjects and thus Finapres systolic pressure measurements would have been lower than those of Imholz and associates (1990) and Jellema and co-workers (1990) who used normotensive subjects with average ages of 30 and 25 respectively.

Finapres estimates of systolic, diastolic and mean arterial pressure have been shown to be highly related ($p < 0.01$) to intra-arterial measures in patients at rest ($r = 0.93$, 0.91 and 0.95 respectively (Van Egmond et al., 1985)) and healthy subjects during positive pressure breathing ($r = 0.97$ {diastolic}, $r = 0.96$ {systolic} (Gradwell, 1993)). The differences noted between arterial pressure and that measured by Finapres appears to be primarily due to the amplification of the arterial pressure wave from the aorta to the periphery and as a result of phasic vasoconstriction and dilatation during arterial pressure perturbations (Van Egmond et al., 1985; Imholz et al., 1988; Gradwell, 1993). Consequently much of the variance noted between intra-arterial and Finapres measure of arterial pressure can be attributed to the difference in measurement sites.

Due to the nature of non-invasive measurement at the periphery during rapid changes in arterial pressure, the use of Finapres for the measurement of absolute pressure for inter-subject comparison is questionable. The reliability of the device for longitudinal or test-retest comparison, however, is high and thus providing the system is used

correctly[26] may be considered suitable for measuring intra-subject changes in arterial pressure over time.

PORTAPRES

The new generation of Finapres, the Portapres, is smaller, portable and has amongst other adaptations an integral hydrostatic pressure compensation column which enables finger pressures to be automatically adjusted to heart level. Fig. L.1 shows aspects of the system incorporated in the assembly produced for the parabolic flight studies. Fig. L.2 (at the end of the appendix) illustrates the system in combination with other elements of the parabolic flight assembly.

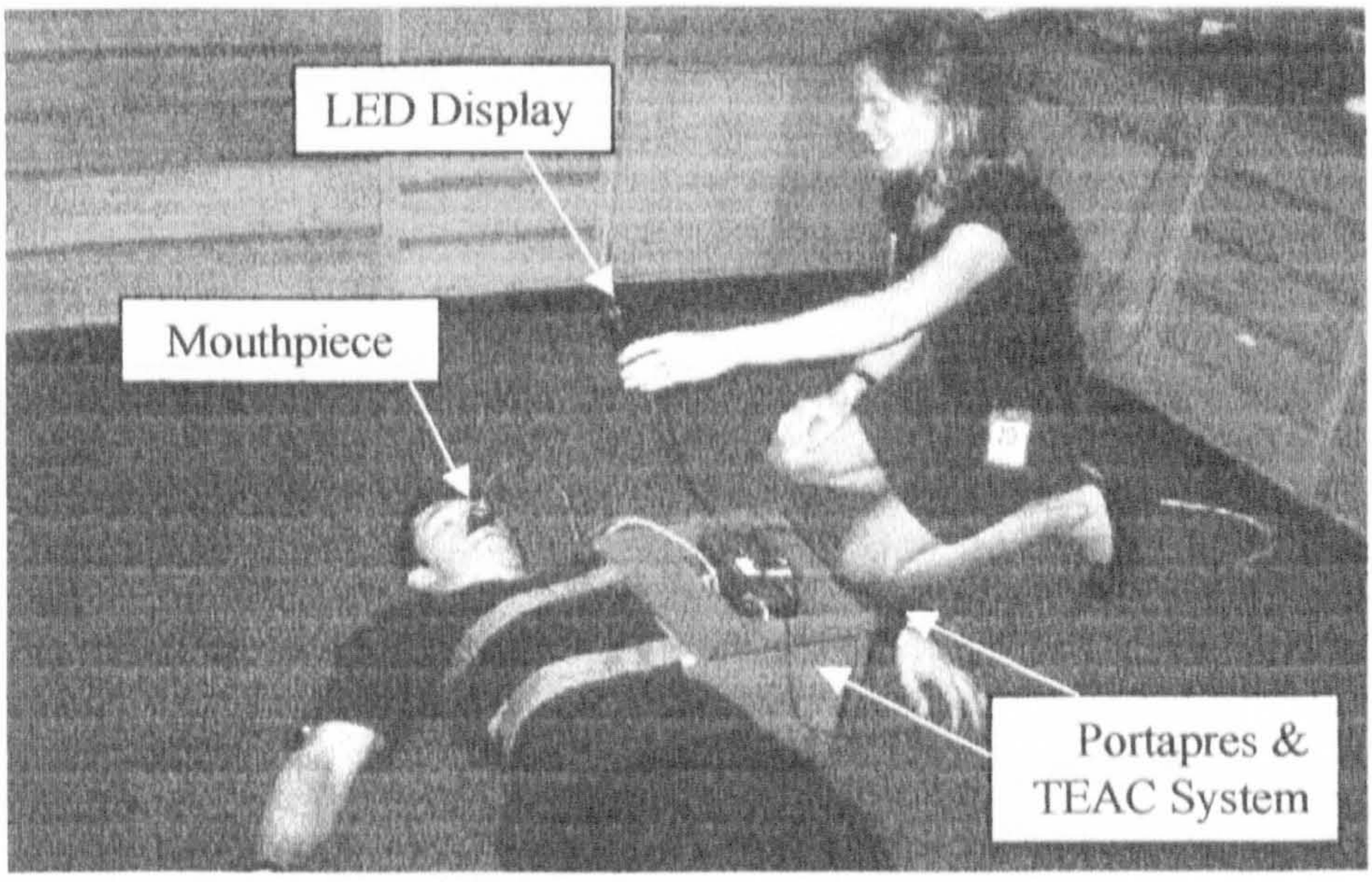


FIGURE L.1, PARABOLIC FLIGHT ASSEMBLY. The Portapres system was assembled with a TEAC magnetic tape recording system and electrocardiogram for the measurement and recording of arterial responses to Valsalva's manoeuvre during parabolic flight. A LED display enabled the subject to monitor expiratory pressure.

Portapres measures arterial pressure using the same principles as Finapres. Preliminary investigations of the accuracy and reliability of the device were undertaken prior to its use for the measurement of arterial pressure on board the European Space Agency's parabolic flights.

Figs L3 and L4 show the relationships between systolic and diastolic arterial pressures respectively taken from Finapres and Portapres. The devices simultaneously measured arterial pressure from adjacent fingers of the same hand of three subjects.

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[26]Day to day Finapres measurement is affected by digit and whole body temperature variations altering arterial constriction and by inappropriate cuff placement.

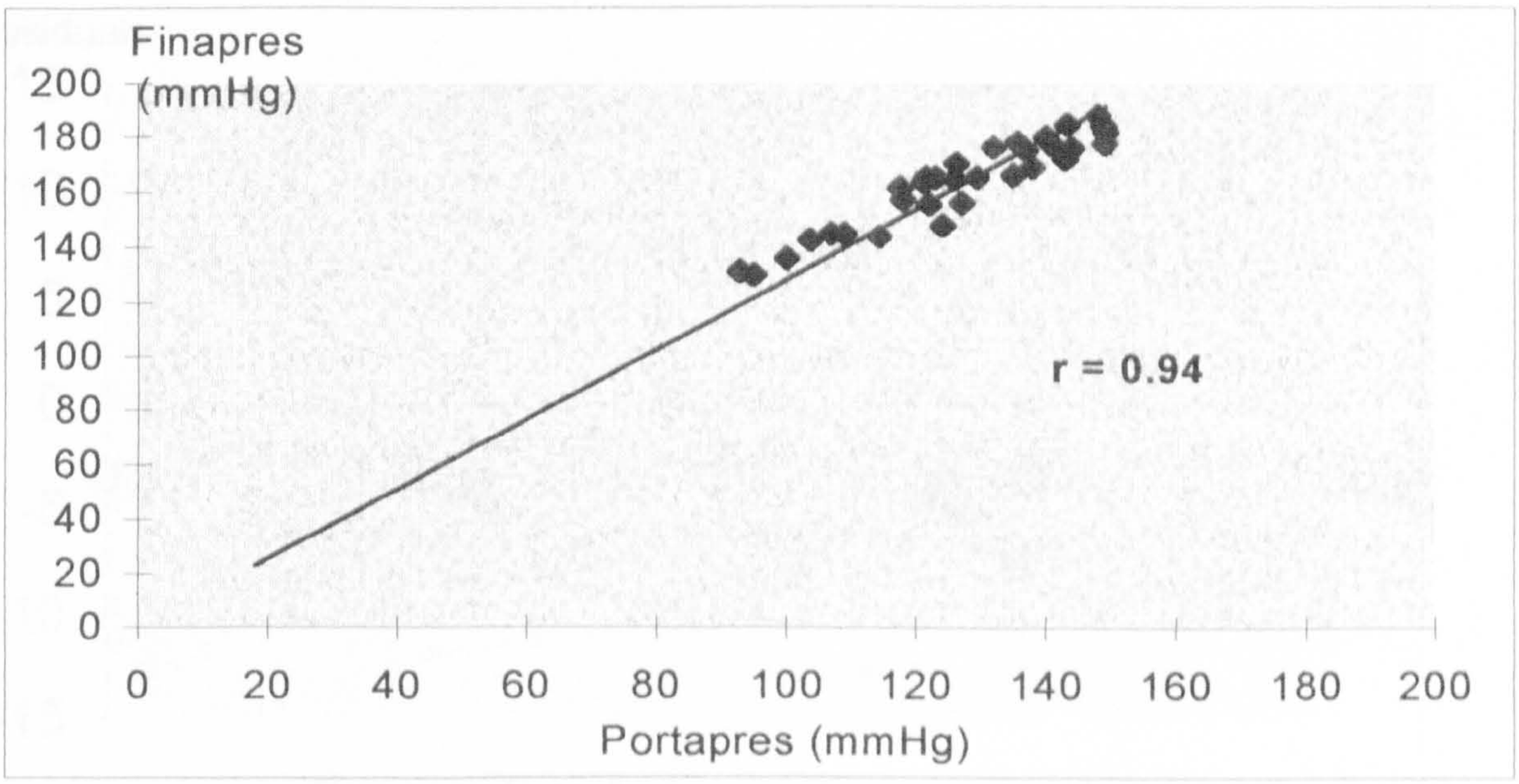


FIGURE L3, STRENGTH OF RELATIONSHIP BETWEEN PORTAPRES AND FINAPRES SYSTOLIC ARTERIAL PRESSURE MEASURES.

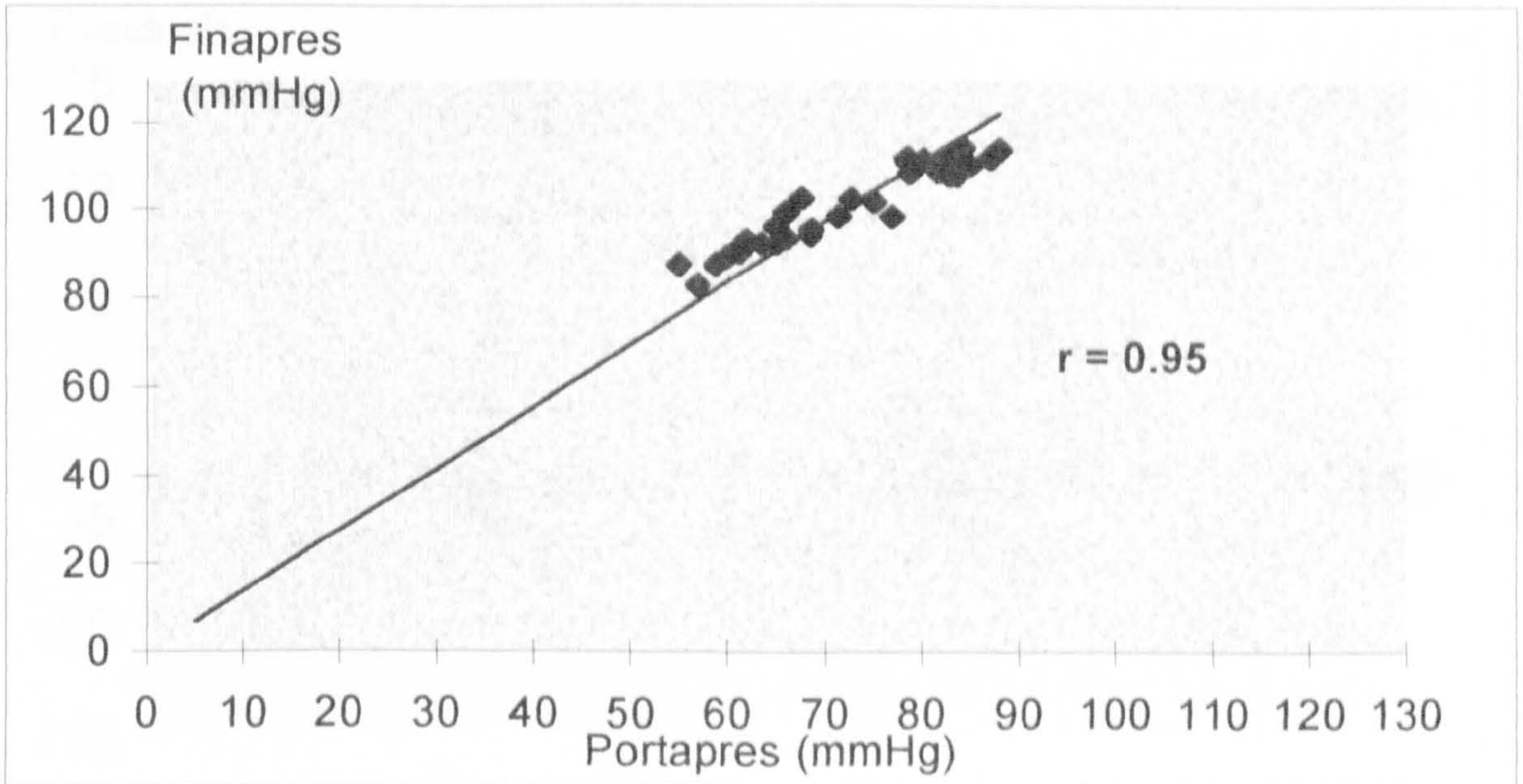


FIGURE L4, PORTAPRES-FINAPRES DIASTOLIC ARTERIAL PRESSURE RELATIONSHIP.

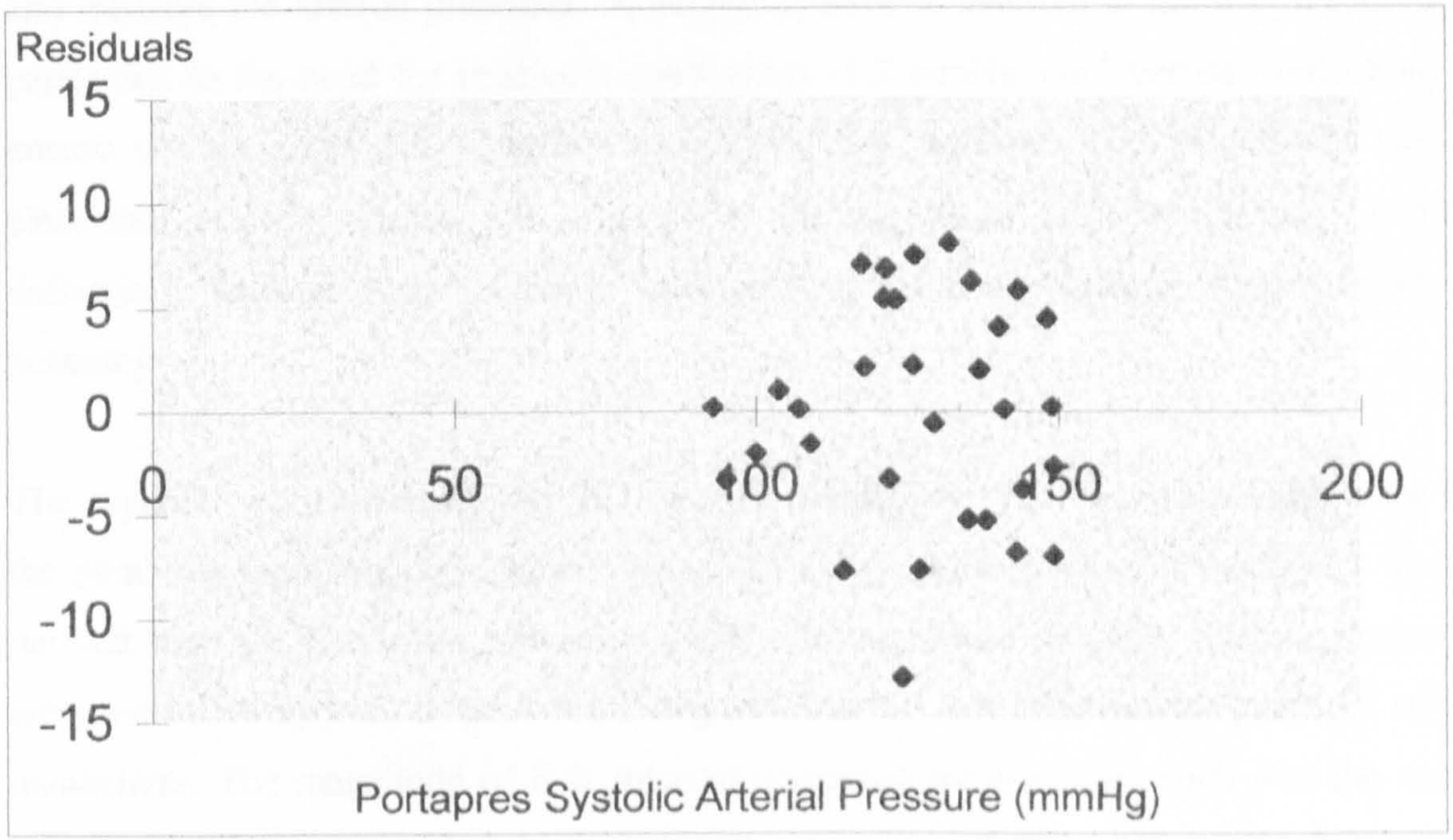


FIGURE L5, PORTAPRES SYSTOLIC ARTERIAL PRESSURE RESIDUAL PLOT

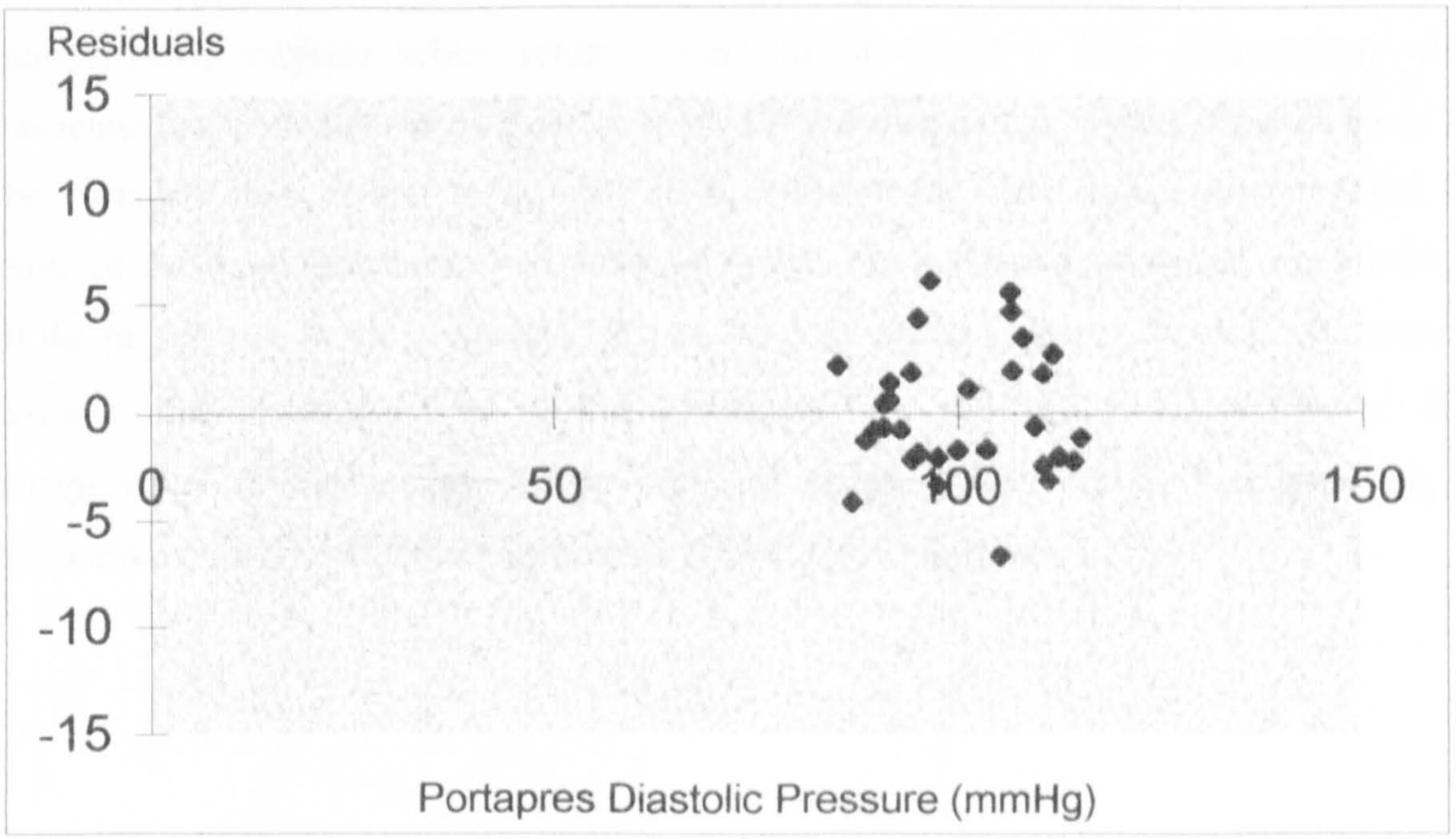


FIGURE L6, PORTAPRES DIASTOLIC ARTERIAL PRESSURE RESIDUAL PLOT. The patterns of residuals reveal that an accurate assessment of the relationships between Portapres and Finapres measures were obtained. Much less variance in Portapres diastolic pressures was noted (essentially ± 5 mmHg of predicted Finapres values) than observed for the systolic measures (± 10 mmHg).

The significant relationships ($P < 0.01$) show Portapres arterial measures to be highly related to those of Finapres, however, the correlations here probably mask the true relationship somewhat due to the fact that thermal recording paper was used to record

and measure the arterial pressures. A degree of error is inherent in the use of recording paper due to the need for relatively small gains (1.3 $mmHg.mm^{-1}$ vertical deflection) to ensure all pressures are recorded from a varying baseline. The subsequent use of electronic means (Maclab 4/e – gains in the region of 0.01 $mmHg.mm^{-1}$ vertical deflection) enabled more accurate measurement with appropriate improvements in accuracy.

The capability to measure change in baroreflex sensitivity was of primary importance for the parabolic flight experimentation. Figure L7 shows a comparison of baroreflex slopes derived from six Valsalva's manoeuvres using Portapres and Finapres. Systolic pressures were measured by both devices according to relative R – R intervals for phase IV of the manoeuvre. The magnitude of R-R interval responses measured by each was the same, however, Finapres recorded higher systolic pressures (+16 mmHg, $p < 0.01$) than Portapres during the post expiratory response. The greater pressures recorded may be due to the tendency for Finapres to measure higher systolic arterial pressures[27] in young normotensive subjects when venous return to the heart is high concomitant with vasoconstricted vascular beds (Imholz et al., 1990; Jellema et al., 1996). This tendency in the Portapres may be less as a result of the refinements in the equipment employed to produce the 'upgraded device' i.e. Portapres might show a less pronounced amplification of the pulse wave at the periphery. Despite the difference in measured systolic pressures, however, the mean slopes of 15.6 ± 2.9 $ms.mmHg^{-1}$ and 19.3 ± 3.3 $ms.mmHg^{-1}$ for Finapres and Portapres respectively were not significantly different, thus indicating a relatively systematic difference in arterial pressure measurement.

[27] Than intra-brachial or radial arterial pressures

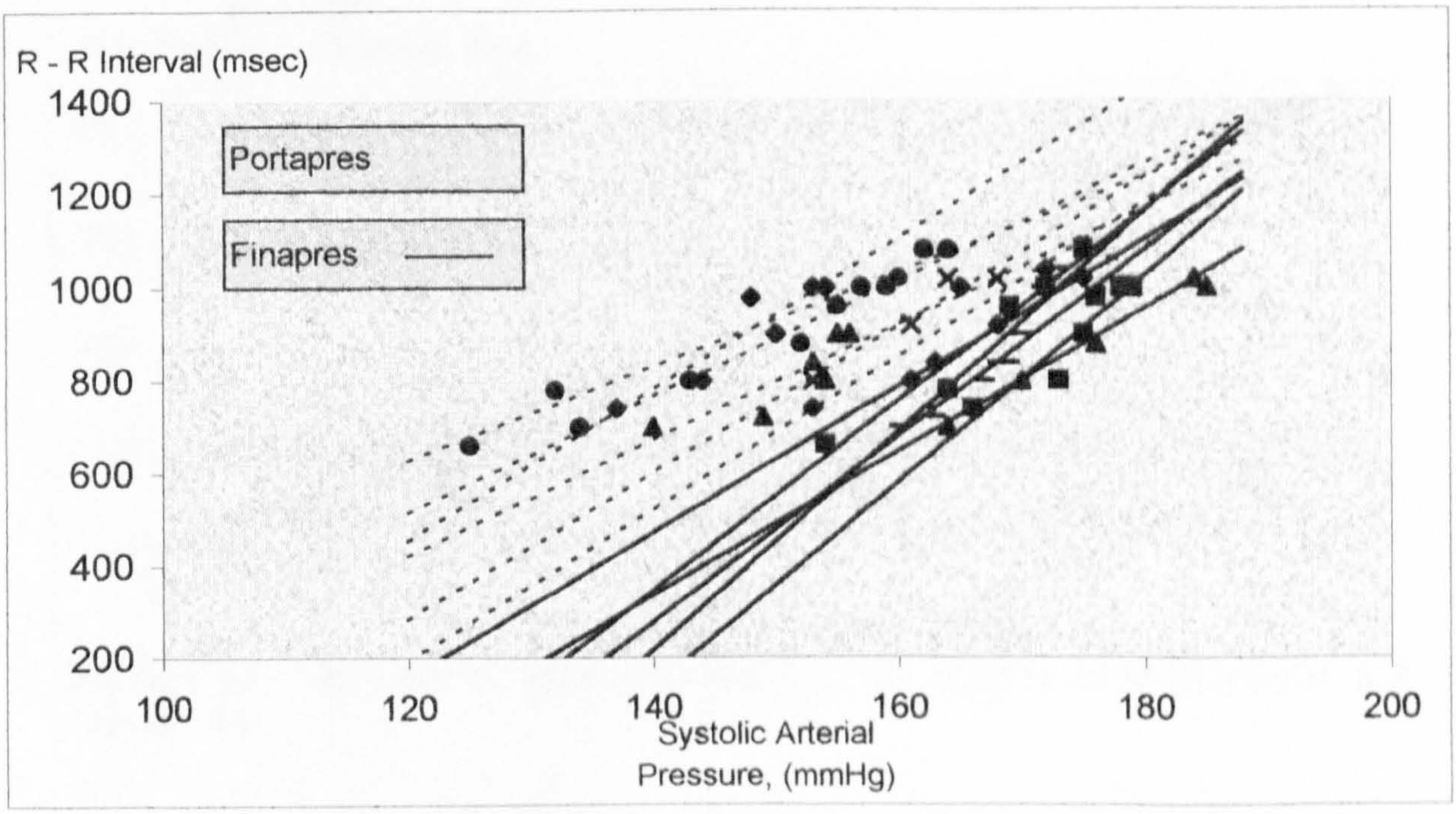


FIGURE L7. PORTAPRES & FINAPRES BAROREFLEX SLOPES. Baroreflex sensitivity slopes derived from phase IV of the arterial response to Valsalva's' manoeuvre. Two manoeuvres were performed by three subjects whilst arterial pressure was simultaneously measured by Portapres and Finapres. The lines of best fit show the similarity between the Portapres dashed) and Finapres (solid) slopes although systolic pressures were measured as significantly greater ($p < 0.01$) by Finapres.

A review of literature related to the reliability of non-invasive arterial pressure measurement by means of the Penaz method indicates that the temporal reproducibility of R-R interval is good (Imholz et al., 1988). Figure L.8 shows cumulative R – R interval as measured by electrocardiogram plotted against R – R interval recorded by means of Portapres. A highly significant correlation of 0.99 was obtained from the data points which were derived from phase IV of six successive Valsalva's manoeuvres (Fig L8).

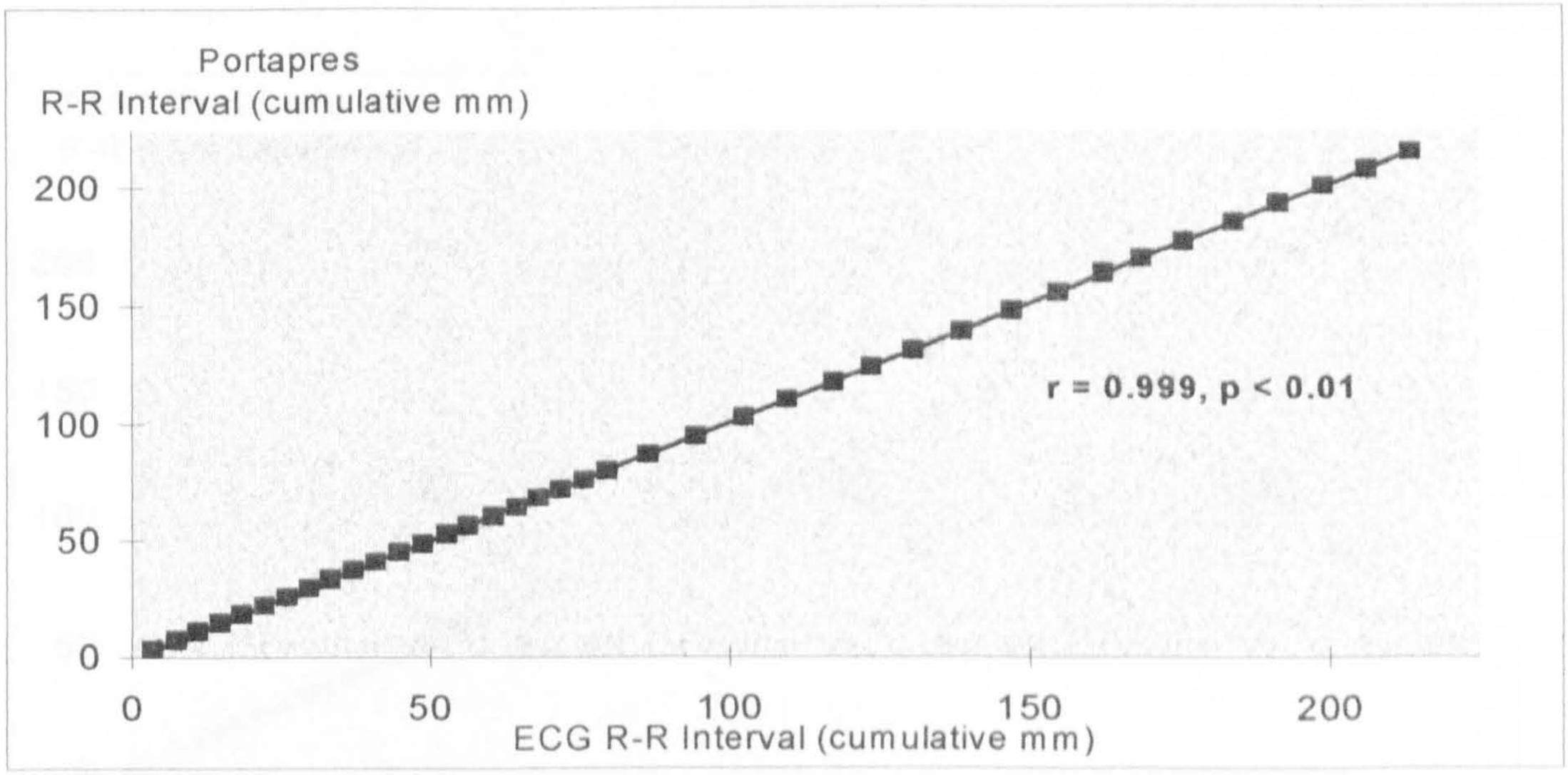


FIGURE L8, PORTAPRES REPRODUCIBILITY OF ELECTROCARDIOGRAM R-R INTERVAL.

For the parabolic flight aspect of the study Portapres measurements of arterial pressure were recorded onto the TEAC HR 10/30 magnetic tape recorder. The TEAC system was designed to record data to 7 channels over a wide range of environmental pressures, vibrations, temperatures and accelerations. To confirm the accuracy and reliability of this system preliminary arterial pressure and electrocardiogram measurements were taken using Portapres and an electrocardiogram respectively. The variables were recorded using the TEAC system and played back for analysis using the TEAC playback unit. Figures L9 and L10 reveal that the data recorder and associated playback unit faithfully reproduced electrocardiogram R – R interval (cumulative) and Portapres arterial pressure.

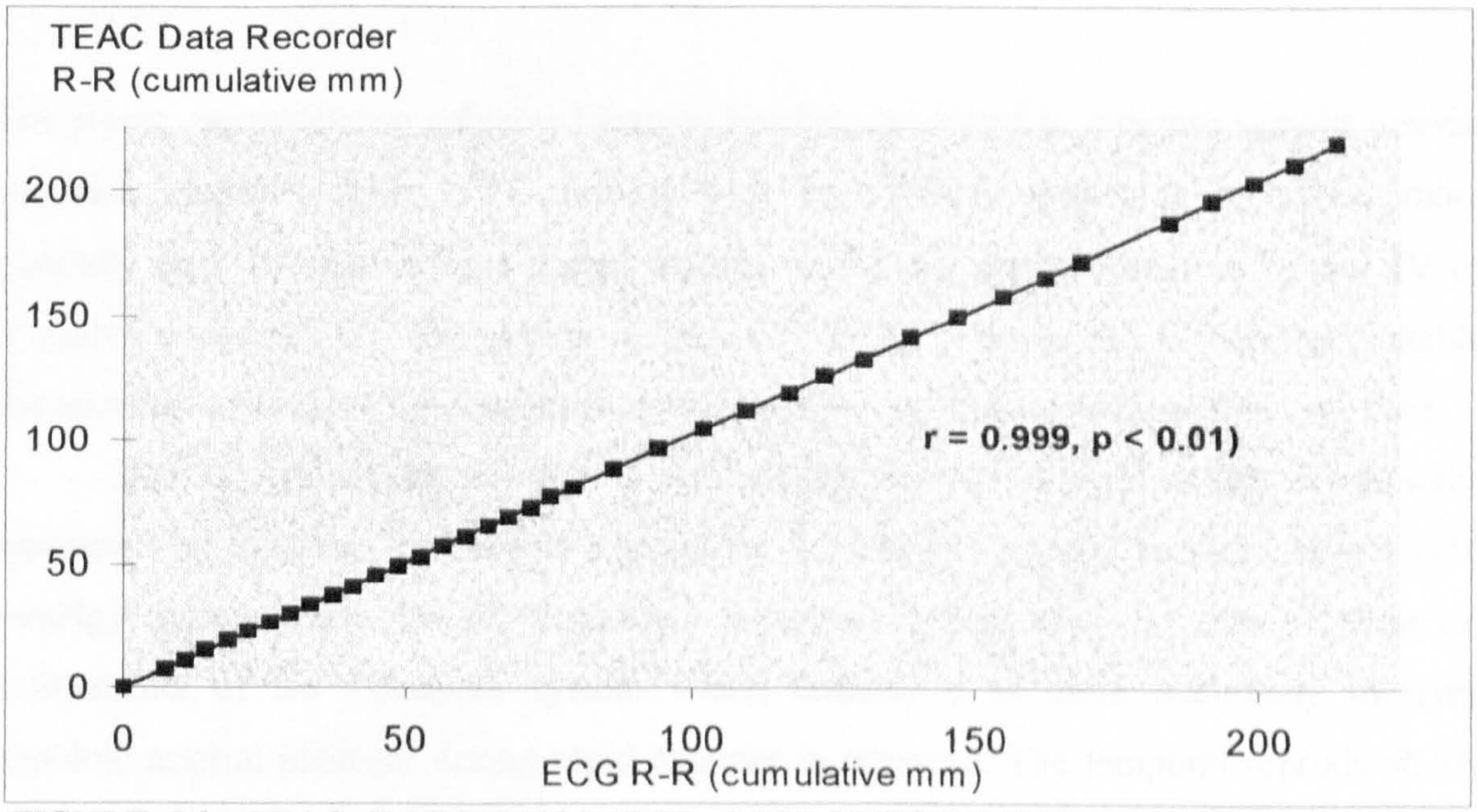


FIGURE L9, TEAC DATA RECORDER REPRODUCIBILITY OF PORTAPRES R-R INTERVAL.

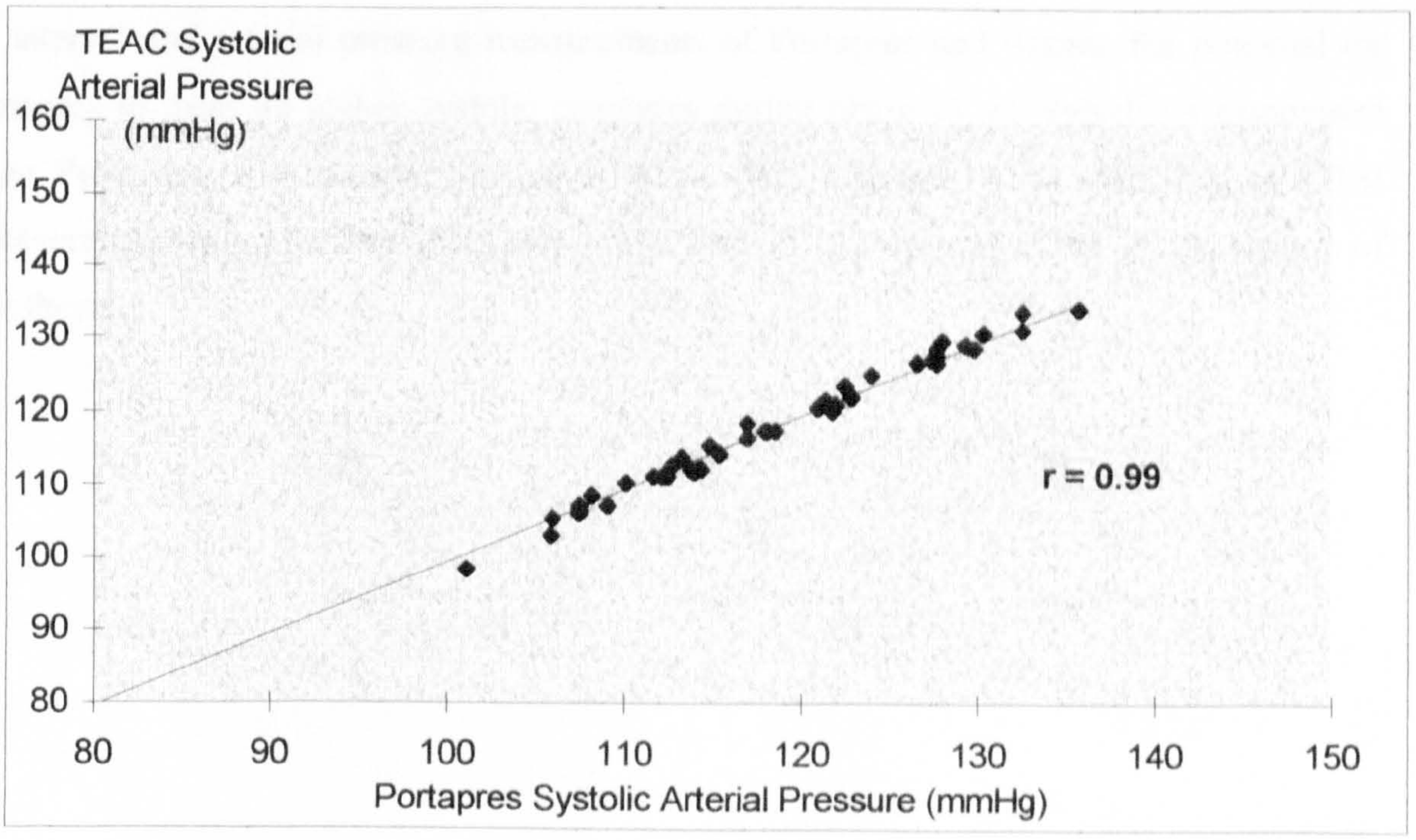


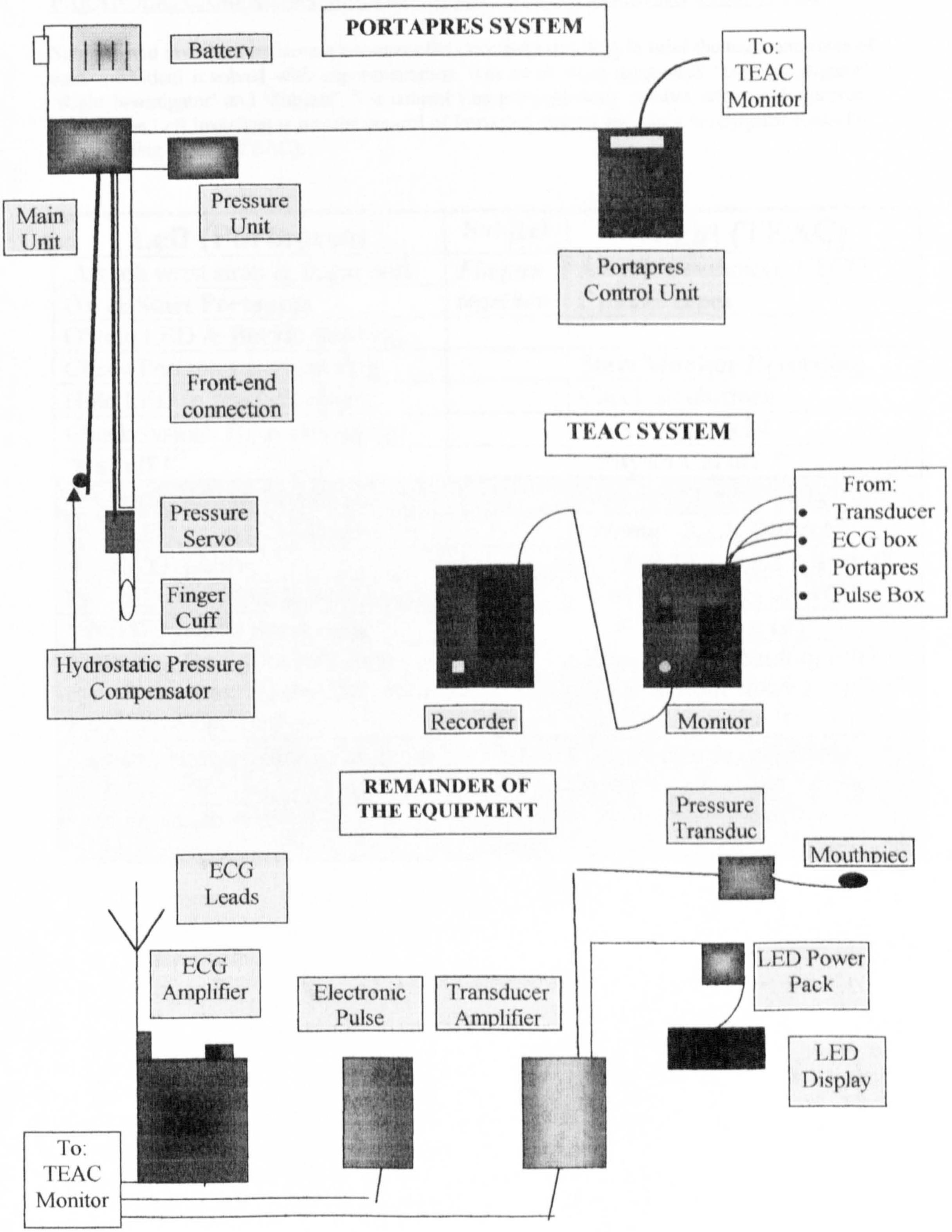
FIGURE L10, TEAC DATA RECORDER REPRODUCIBILITY OF PORTAPRES SYSTOLIC ARTERIAL PRESSURE.

SUMMARY

For young, normotensive subjects Finapres has been reported to measure systolic arterial pressure slightly higher (+11 mmHg) than intra-arterial pressures measured more centrally (e.g. brachial artery) during rapidly increasing arterial pressure (phase IV of Valsalva's manoeuvre). The system is, however, highly reliable and is therefore suitable for accurate assessment of changes in intra-subject arterial pressure measures over time.

The Portapres system is able to accurately reproduce changes in arterial pressures measured by Finapres, but shows a tendency to measure systolic pressures lower (-16 mmHg) during phase IV of Valsalva's manoeuvre. This may be due to technical refinements of the Portapres system which enables it to more accurately measure absolute arterial pressure during rapid changes in pressure. The temporal reproducibility of Portapres R-R interval measures using the electrocardiograph as the criterion measure, is highly reliable. The TEAC recording and playback system faithfully reproduces the R-R interval and arterial pressure measurements of Portapres and despite the potential for Finapres to measure higher systolic pressures during phase IV of Valsalva's manoeuvre than Portapres, the measurement of BRSI is little affected. The reliability of BRSI measurement using the Portapres and TEAC system is presented in the results section of the thesis.

FIGURE L.2, PARABOLIC FLIGHT RECORDING AND MONITORING ASSEMBLY



APPENDIX M

PARABOLIC CAMPAIGN IN-FLIGHT SUBJECT AND INVESTIGATOR TASKS

Subjects and investigators wore a waterproofed crib sheet detailing in brief the tasks and roles of each individual involved with experimentation. The roles were designated 'Left Investigator', 'Right Investigator' and 'Subject'. The subject was predominantly passive, whereas the primary task for the Left Investigator was the control of Portapres and for the Right Investigator control of the recording system (TEAC).

Left (Portapres)	**Subject**	**Right (TEAC)**
Attach wrist strap & finger cuff.	***Fingers together***	**Attach** mouthpiece + ECG.
On & Start Portapres		**Change tapes**
Obtain LED & Buckle webbing.		
Check Portapres is measuring.		**Start Monitor Recording**
Hold LED in front of subject		Check all channels
Check systolic BP is increasing		Back to channel 4
"**Cal off** !" *1.8G*		" **Physio Cal off** ?" *1.8G*
'G' Meter - **" NOW, zero G"**		Listen out for "**NOW..**"
Hold LED, Watch 'G' Meter		**"*Name*' 3,2,1, Blow..!"**
Watch 'G' Meter		**" ...9,8,7,6,5,4,3,2,1, stop !"**
Put LED back. Check Systolic BP		Watch 'G' Meter for **+G !**
" NOW systolic decreasing"		**"NOW positive G !"**
Portapres OFF *if subj change over is to occur. If same subj then put* ***Physio Cal*** *back on.*		***Stop TEAC recording after*** *"Now systolic decreasing" if subj change over is to occur.*
Loosen wrist strap & unclip finger cuff.	Undo ECG	Unclip mouthpiece & place in subject's lower left leg pocket.
Unclip your leg strap	Undo leg strap	Unclip your leg strap

Biomedical Sciences Division
Physiology Group

KING'S College LONDON
Founded 1829

APPENDIX N

MOVEMENT ORDER TO/FROM BORDEAUX

All Study Volunteers,

15 Oct 1998

Campden Hill Road
London W8 7AH
Tel 0171-333 4230
(Group Office)
Fax 0171-333 4008

Admin and Move to/from Bordeaux.

Hello again semi-astronauts,

Everyone has devoted a great deal of time and energy (!!) to the project over the last 12 months and I am very grateful. The final flights are upon us, the study is close to fruition and it goes without saying that I couldn't have done it without you (Prof and I would look very silly measuring the baroreflex response of an empty couch !).

We'll have two new faces with us this time, Phil Pollard, whom some of you have met, and Tim Jones.

As you know Tomorrow's World will also be down in Bordeaux for a couple of days in order to get some footage for their double feature. They will be involved with flight 1 but are also trying to get on flight 2.

Otherwise things are pretty much the same as last time, the details of which are contained within.

1. **Food and accommodation:**
   - 2 or 4 berth self-catering apartments.
   - As before all of their apartments come with double beds only so sleeping bags might be a good idea again.
   - £11 per head per day for food.
   - The apartments are in Bordeaux and 10 minutes from the airbase we'll be working from (Imotel once again).

   In order to keep our car hire costs to a minimum I have booked us into a hotel opposite the train station for the last night (Fri) which will mean we will not need to have transport to get us to Bordeaux station on the Saturday.

2. **Transportation:**
   - By Eurostar/TGV from Waterloo station, London, via Lille to Bordeaux.
   - See Annex A for times and dates.
   - Julian Proudfoot and I will be leaving in advance (22nd Oct) to set up equipment. We'll be hiring a car and will pick you up from Bordeaux station on the day you arrive.

- Richard Wells (0171 251 0583) will act as the contact person just before departure if there are any problems and will sort out any difficulties during the journey.
- Your tickets have been booked and will be sent to you next week.
- **Baggage**: Maximum allowable = 2 suitcases and one piece of hand luggage per person.

1. **Kit List**: See Annex B.

2. **Contact address & number** in France, maps etc : See Annex C.

3. **Schedule and flight details**: See Annex D.

4. **KCL study Personnel** (complete as of 15/10/97): See Annex E.

This is not an exhaustive list but it does cover all essentials. Any other information that needs to be passed on to you between now and then will be done by phone as I receive it.

Yours,

Annex A

Train Date and Time Departure/Arrivals

London, Waterloo	**Lille**	**Bordeaux**	**Name**
Thur 22nd Oct			
			4 x Standard
08.27	11.29		*Evetts, Johnstone*
	12.21	17.51	*Proudfoot, Free*

Returning.

Bordeaux	**Lille**	**London**
Sat 31st Oct		
08.02	13.04	
	13.42	14.43

London, Waterloo	**Lille**	**Bordeaux**	**Name**
Sat 24th Oct			
			3 x Standard
14.23	17.21		*Jones, Wells,*
	17.53	23.08	*Pollard*

Returning.

Bordeaux	**Lille**	**London**
Sat 31st Oct		
08.02	13.04	
	13.42	14.43

London, Waterloo	**Lille**	**Bordeaux**	**Name**
Sat 24th Oct			
			1 x Excursion
14.23	17.21		*Turner*
	17.53	23.08	

Returning.

Bordeaux	**Lille**	**London**
Wed 28th Oct		
08.02	13.04	
	13.42	14.43

NB: Remember guys, we have to be there AT LEAST 20 minutes before departure (G-man that means 40 mins for you !!)

Annex B

Equipment and Important Items of Clothing

1. **Passport.**
2. Cotton T-shirt(s).
3. Comfortable trousers for under your flight overalls.
4. White soled trainers.
5. Pen & pad (with some form of pocket tether).
6. Cameras (with wrist tether).
7. Tether for glasses.
8. Sports gear (I would like most of us to do a shuttle run to estimate our fitness at some point).
9. Sense of humour (mandatory) !

Annex C

5.3 Useful telephone numbers

NOVESPACE - PARIS
Tél : 33 (0)1 42 33 41 41
Fax : 33 (0)1 40 26 08 60

NOVESPACE - BORDEAUX
Tél : 33 (0)5 56 34 05 99
Fax : 33 (0)5 56 34 06 09
GSM : 33 (0)6 08 90 90 92

Experimenters phone number when at Novespace Bordeaux : 33 (0)5 56 34 06 40

BORDEAUX-MERIGNAC AIRPORT

AIR FRANCE :	0 802 802 802
AIR LIBERTE :	05 56 34 53 53
AIR LITTORAL :	05 56 47 62 62
BRITISH AIRWAYS :	05 56 47 63 91
REGIONAL AIRLINE :	05 56 34 50 76
SABENA :	05 56 34 28 11
Passenger Information :	05 56 34 50 50

CAR RENTALS

ADA :	05 56 34 23 32
Avis :	05 56 34 38 22
Budget France :	05 56 47 84 22
Citer :	05 56 34 20 68
Europcar :	05 56 34 05 79
Euro-Rent :	05 56 34 08 15
Hertz :	05 56 34 18 87

TAXIS

Taxis-radio Mérignac : 05 56 97 11 27

How to go to the Sogerma - Mérignac / Bordeaux - France :

The campaign will take place on the SOGERMA base located on the Bordeaux-Mérignac Airport in the Mérignac city.

Mérignac is located in the south western suburb of Bordeaux.

Address (For peoples and equipments) :

SOGERMA - SOCEA / NOVESPACE
Essais en Vol
Vols Paraboliques - A300
Bordeaux Aéroport
Avenue Marcel Issartier
BP 2
33701 Mérignac Cedex
France

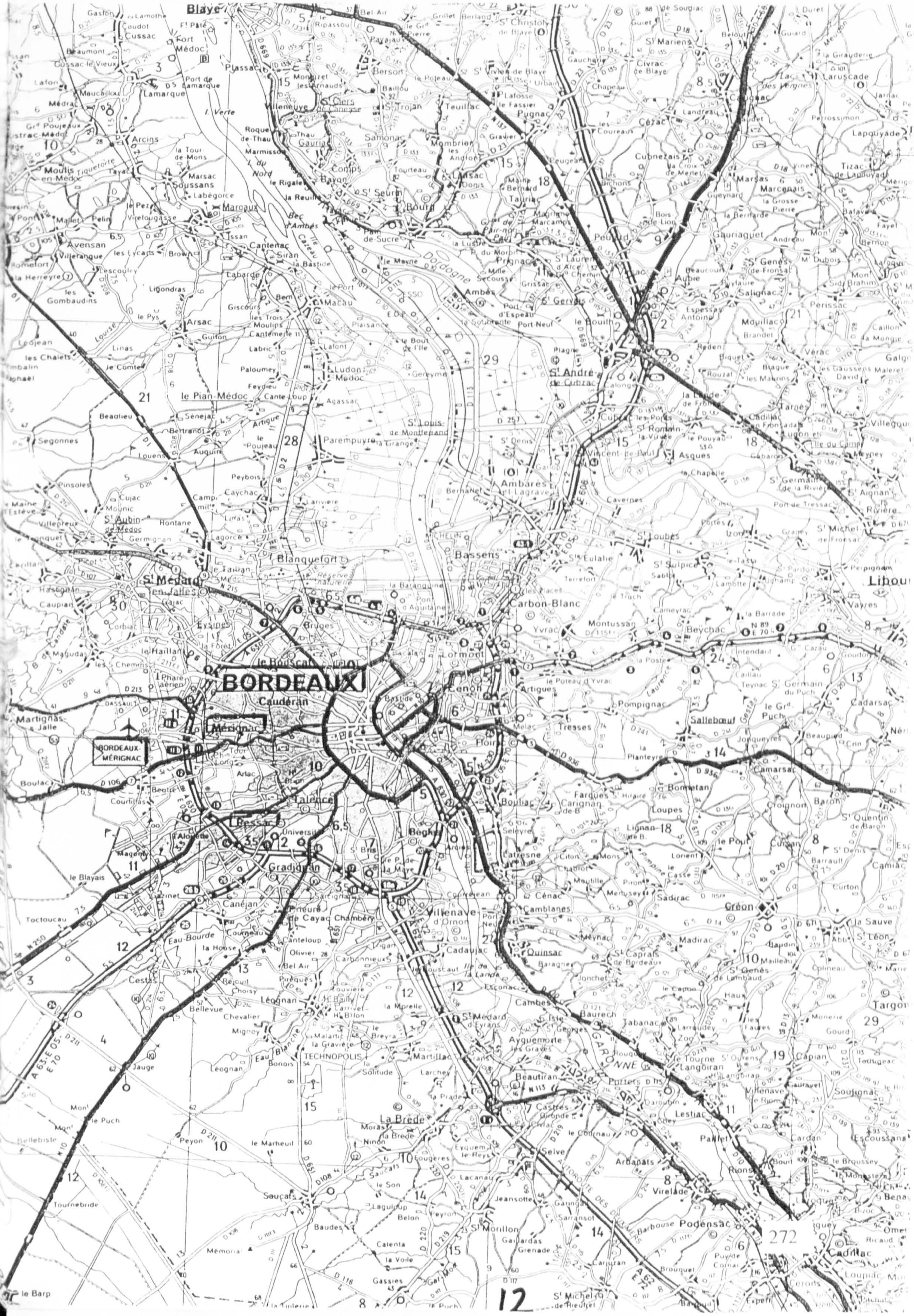
Hotel Address :

For persons staying at the **IMOTEL**, the address is :

1, allée des Isatis
33700 Mérignac
France
Tel : (33) 05 56 13 38 38
Fax : (33) 05 56 55 93 26

It is located about 10 min by car from the Sogerma A300 parking.

For **Mobile** number see over-leaf.


Blaye
Gaston
Lamothe
Coudot
Cussac
Ft Pâté
Fort Médoc
Beaumont
Cussac le Vieux
Lafon
Port de Lamarque
Maucaillou
Lamarque
Médrac
Gd Poujeaux
Arcins
la Tour de Mons
Moulis Tiquefortе
Tayac
Marsac
Soussans
Labégorce
le Pez
Margaux
Mallet
Pelin
Virelougasse
Avensan
Villeranque
les Lycarts
Brown
Romefort
la Herreyre
Lescouley
les Gombaudins
Ligondras
Cantenac
Siran
la Bastide
Labarde
Issan
Giscours
le Pys
Arsac
les Trois Moulins
Cantemerle
Guilon
Leojean
Linas
les Chalets
le Comte
Louise
le Pian-Médoc
Cante Loup
Agassac
Ludon Médoc
Labrie
Paloumey
Feydieu
Gereyme
Lafont
le Bout de l'Ile
Plaisance
Beaulieu
Senejac
Bertrand
Segonnes
Auguin
Louens
Artigue
le Poujeau
Parempuyre
la Grange
St Louis de Montferrand
Pinsoles
Cujac
Mounic
St Aubin de Médoc
Villepreux
Hontane
Germignan
Lagorce
Caychac
Peybois
Larivière
Linas
Picot
Blanquefort
le Tailan
St Médard en Jalles
Hastignan
Caupian
Eysines
Bruges
Corbiac
le Haillan
la Forêt
le Bouscat
BORDEAUX
Caudéran
Mérignac
Phare aérien
Martignas-s-Jalle
BORDEAUX-MÉRIGNAC
Boulac
Beutre
Courtillas
Artac
Tour Chin Long
Talence
Pessac
Gradignan
le Blayais
Canéjan
Toctoucau
Eau-Bourde
la House
Cestas
Bel Air
Pirèques
Choisy
Léognan
Bellevue
Chevalier
Mignoy
Eau Blanche
Bonois
TECHNOPOLIS
la Solitude
Martillac
Larchey
Jauge
Tournebride
le Barp
Saucats
Lagulisup
Belon
Peyron
Baudes
Mémorial
Calenta
la Voile
Gassies
la Tuilerie
Le Puch
Peyon
le Marheuil
Ninon
la Brède
Moras
La Brède
Ayguemorte-les Graves
St Médard d'Eyrans
St Michel de Rieufret
Baurech
Cambes
Tabanac
Beychac
Yvrac
Montussan
Pompignac
Artigues
Cenon
Floirac
Bègles
Villenave d'Ornon
Cadaujac
Carbonnieux
Canteloup
Olivier
Bel Air
Pirèques
Léognan
Martillac
Beautiran
Castres Gironde
Portets
Langoiran
Le Tourne
Cadillac
Podensac
Barbouse
Quinsac
Loupiac
Omet
Ricaud
Targon
Soulignac
Lestiac
Cardan
Escoussans
Arbanats
Virelade
Rions
Pailet
Selve
Jeansotte
Garrigat
Sarransol
St Morillon
Gardardas
Grenade
Caruiran
Brouquet
Puy de Cornac
Cérons
Bazaut
St Michel de Rieufret
Lacanau
Eyquem
le Reys
Sougères
Saucats
le Son
Calenta
la Voile
Gassies
la Tuilerie
le Puch
Mont
Bellebiste
Tournebride
Peyon
le Marheuil
Ninon
la Brède
Moras
La Brède
Castres Gironde
Portets
Beautiran
Langoiran
Le Tourne
Cadillac
Podensac
Loupiac
Omet
Ricaud
Targon
Soulignac
Lestiac
Cardan
Escoussans
Arbanats
Virelade
Rions
Pailet
Selve
Jeansotte
Garrigat
Sarransol
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Gardardas
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Eyquem
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Ninon
la Brède
Moras
La Brède
Ayguemorte-les Graves
St Médard d'Eyrans
St Michel de Rieufret
Baurech
Cambes
Tabanac
Beychac
Yvrac
Montussan
Pompignac
Artigues
Cenon
Floirac
Bègles
Villenave d'Ornon
Cadaujac
Carbonnieux
Canteloup
Olivier
Bel Air
Pirèques
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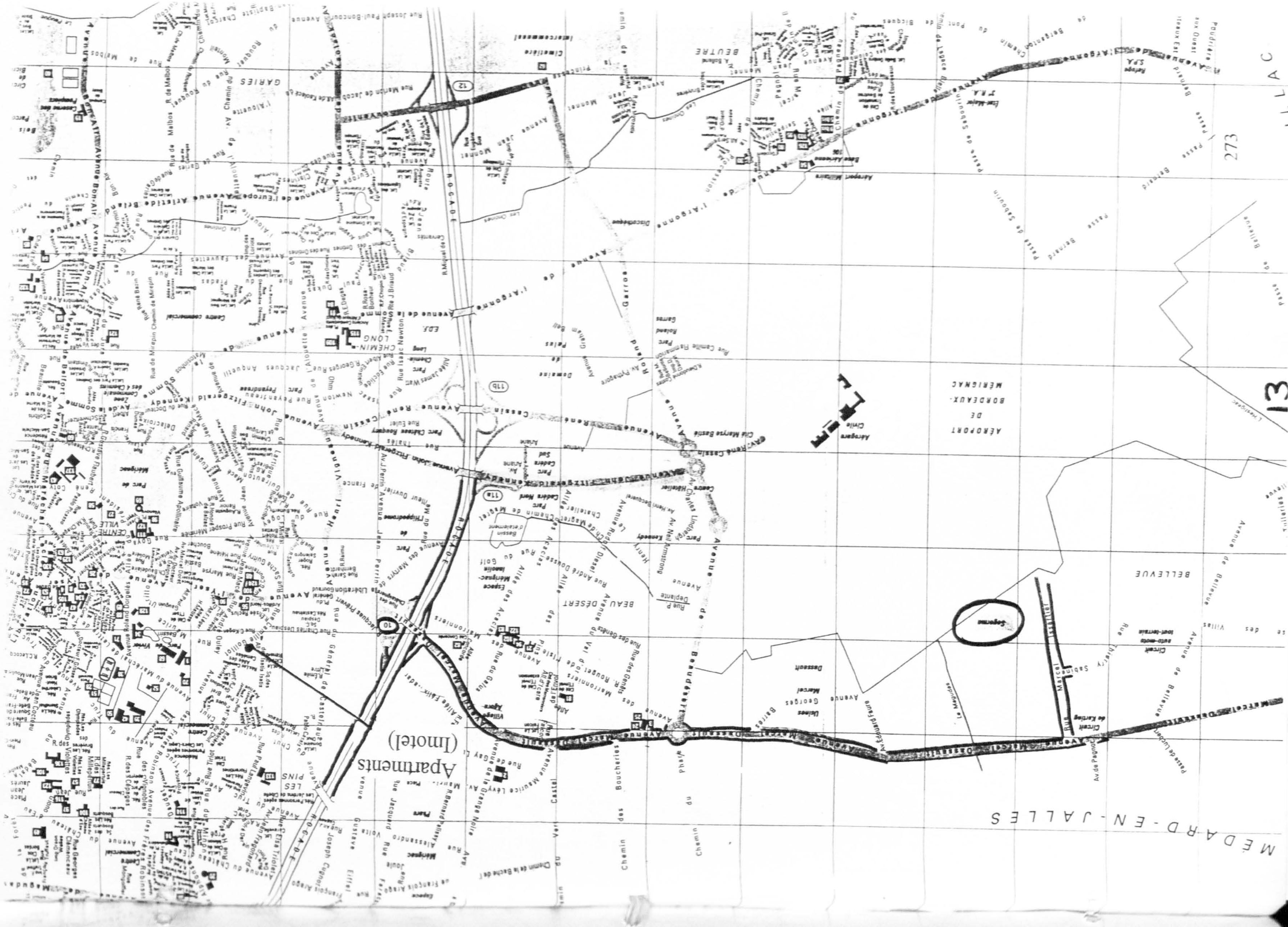
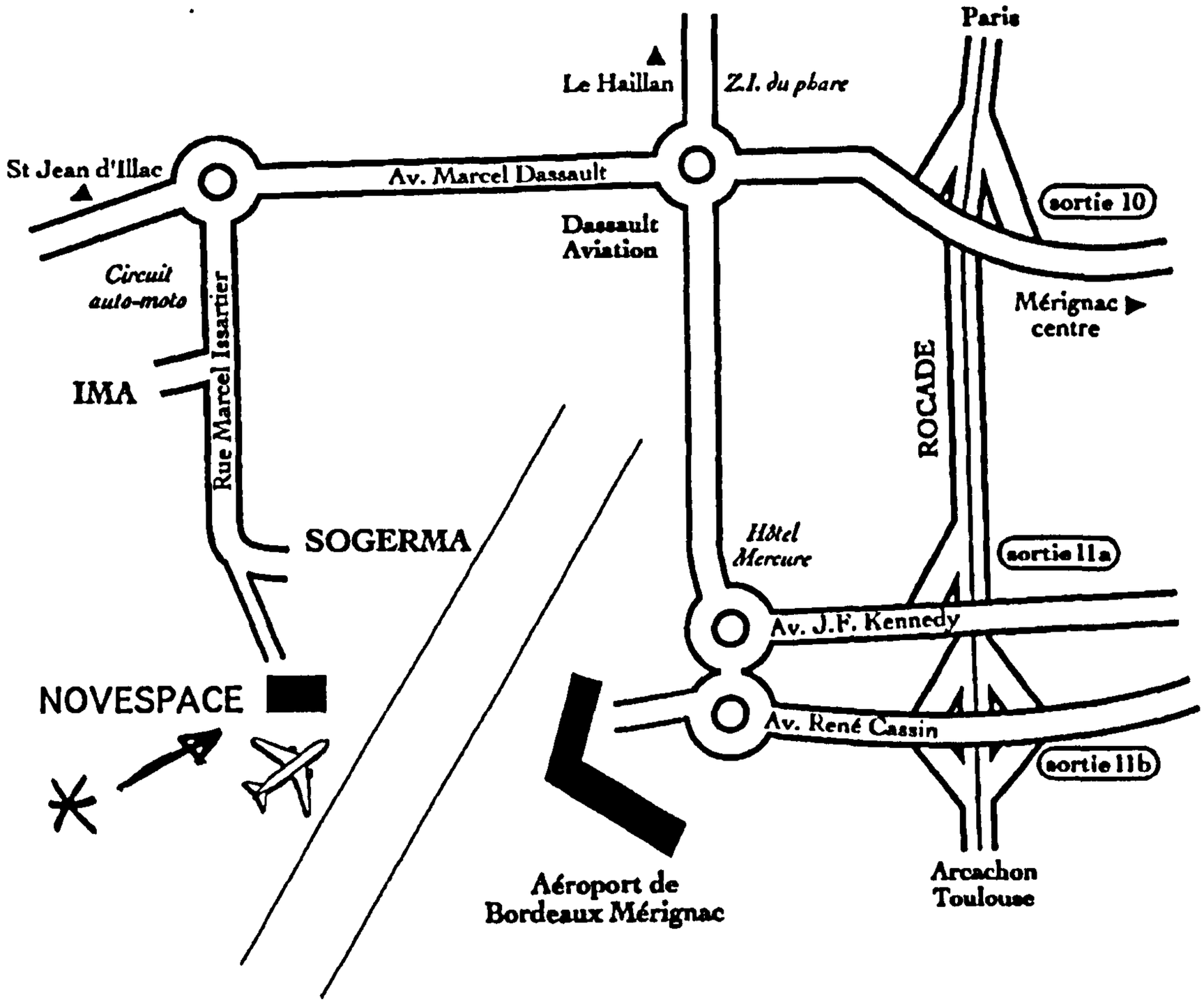
Portets
Langoiran
Le Tourne
Cadillac
Podensac
Barbouse
Quins


Apartments
(1motel)
MEDARD-EN-JALLES
AÉROPORT
DE
BORDEAUX-
MÉRIGNAC
BEAUDESERT
BELLEVUE
GARIES
BEUTRE
CHEMIN-LONG
Avenue de l'Argonne
Avenue de la Libération
Avenue de l'Europe
Avenue Bon-Air
Avenue Jean Monnet
Avenue Rene Cassin
Avenue John-Fitzgerald Kennedy
Avenue de Belfort
Avenue du Maréchal Leclerc
Avenue de Bellevue
Route de Toulouse
Route de Bayonne
Rue Miguel de Cervantès
Rue Jean Jaurès
Rue Jean Mermoz
Rue Jean Moulin
Rue Victor Hugo
Rue Jean Rostand
Rue Jean Jacques Rousseau
Rue Jean Bart
Rue Jean Mermoz
Rue Jean Moulin

5 MAPS AND USEFUL NUMBERS

5.1 Access Map to Novespace



Annex D.

FLIGHT DAYS: Tuesday 27 Oct – Thurs 29 Oct 1997

Time	Detail/location	Action
05.15	Evetts/Proudfoot meet outside apartments.	Evetts/Proudfoot
05.30	**Project Office at airbase.**	
05.30 - 06.15	Pre-flight equipment checks and calibrations	Evetts/Proudfoot
06.15	Flight team for that day meet outside apartment - pick up by Evetts	Flight team Evetts
06.30	Personal preparation for flight (electrodes, fight-suits etc)	Flight team Evetts
06.45 - 07.45	Baseline Valsalva measurements (20 mins per subject)	Evetts/Proudfoot
07.45 - 08.15	Kit prep and final rehearsals	All
08.30	Meet at **hanger.**	All
08.30 - 09.00	Final equipment checks	Proudfoot
09.00 +	FLIGHT...	

Annex E

Study Personnel and Responsibilities.

Name	Role/career/areas of interest
Simon Evetts	- Project Principle Investigator.
Julian Proudfoot	- Project Technician.
Lisa Johnstone	- State registered nurse - Project Medic.
Graham Free	- Environmental studies and cooking.
Jake Maule	- Gene therapy post-grad now at the International Space University.
Irene Turner	- Sports Science and now physiotherapy under-grad.
Richard Wells	- National Sports Medicine Institute chief executive - IT type person
Tim Jones	- Ex-army officer now working for BT Defence
Phil Pollard	- Sports Studies and now in the Police.

Flight Detail:

Flight 1:

Evetts - Principle Experimenter
Turner
Maule

Craig Doyle from the BBC

Flight 2:

Evetts - Principle Experimenter.
Johnstone
Pollard

Flight 3:

Wells - Principle Experimenter.
Free
Jones
Proudfoot as technical support (TBC)

ASSESSMENT OF THE RELIABILITY AND VALIDATION OF THE USE OF PLASTIC NECK CUPS FOR STIMULATION OF THE CAROTID SINUS.

The aim of the study was to examine the effectiveness of the use of neck cups (Cups) for stimulating the carotid sinus as compared to a traditional lead collar (Eckberg) and a silicone rubber collar of the Sprenkle design (Sprenkle). Two objectives were set; firstly to ascertain whether the Cups would elicit similar responses, as measured by change in R-R interval, to those derived from Eckberg and Sprenkle collars and secondly to examine whether the neck Cups were as reliable as the other devices.

Method. Signed consent was given by 7 males and 5 females (mean age 26.4 ± 5.5 yr) to undertake the study. Subjects were assigned to the study if they showed an asymptomatic response to the application of neck pressure of –60 mmHg. Fig. O.1 illustrates the breakdown of subjects according to the device used. The subjects were allocated to Eckberg *vs* Cups (n = 8) or Sprenkle *vs* Cups (n = 8) comparison groups. The responses to a single train of stimuli for all three devices were ascertained from four subjects and the responses to four trains of stimuli from each device was ascertained from two subjects.

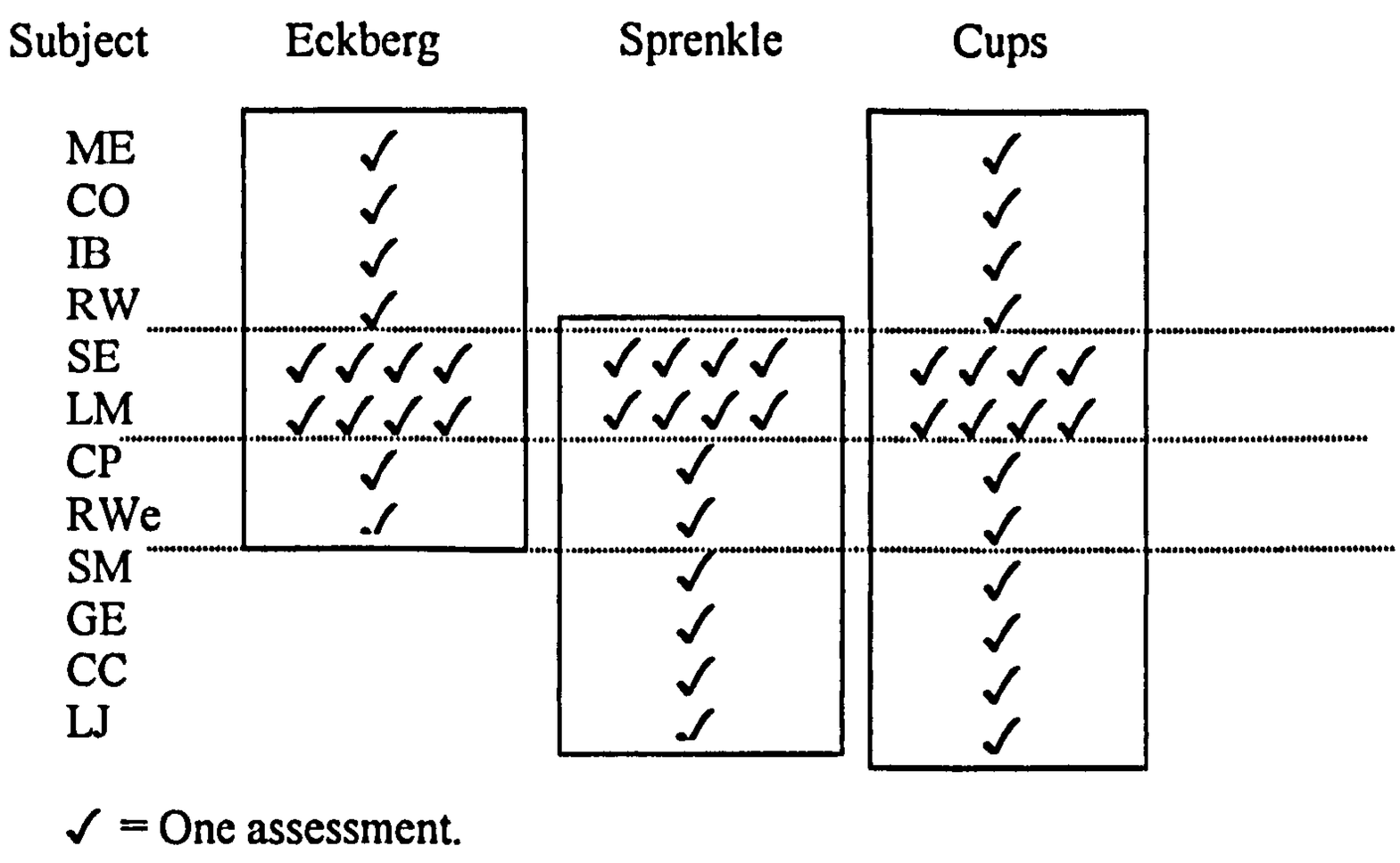


FIGURE O.1 SUBJECT SUBDIVISION ACCORDING TO THE FREQUENCY AND TYPE OF CAROTID SINUS STIMULATION DEVICE. Eight subjects had carotid baroreflex function assessed using neck Cups and Eckberg collar. Eight subjects had carotid baroreflex function assessed using neck Cups and Sprenkle collar. Four subjects had carotid baroreflex function assessed using neck Cups, Sprenkle and Eckberg collars. Two subjects had carotid baroreflex function assessed 4 times using all three devices.

Fig O.2 shows two Cups, the lead 'Eckberg' collar (rear left) and the 'Sprenkle' collar (rear right). Fig O.3 shows subject RWe wearing the Cups attached by a canvas sling. The procedure was similar to that used in the primary study. Stimuli were applied during expiration whilst breathing normally at rest. The stimuli were applied for 0.6 s, 0.75 s before the anticipated 'P' wave, at rates exceeding 400 $mmHg.s^{-1}$. An interval of at least 10 s was given between each stimulus. Between 10 and 16 stimuli comprised a train of pressures and 5 or 6 trains of different pressures were applied for each device. Subjects undertook carotid baroreflex function measurement using two devices during any one experimental period. The order of the use of devices was randomised between subjects as was the order of pressure applications. The order of pressure applications within subjects, however, was not changed. For those subjects who undertook measurements using all three devices or more than one measurement for one device the experimental periods were at the same time of day, but on different days.

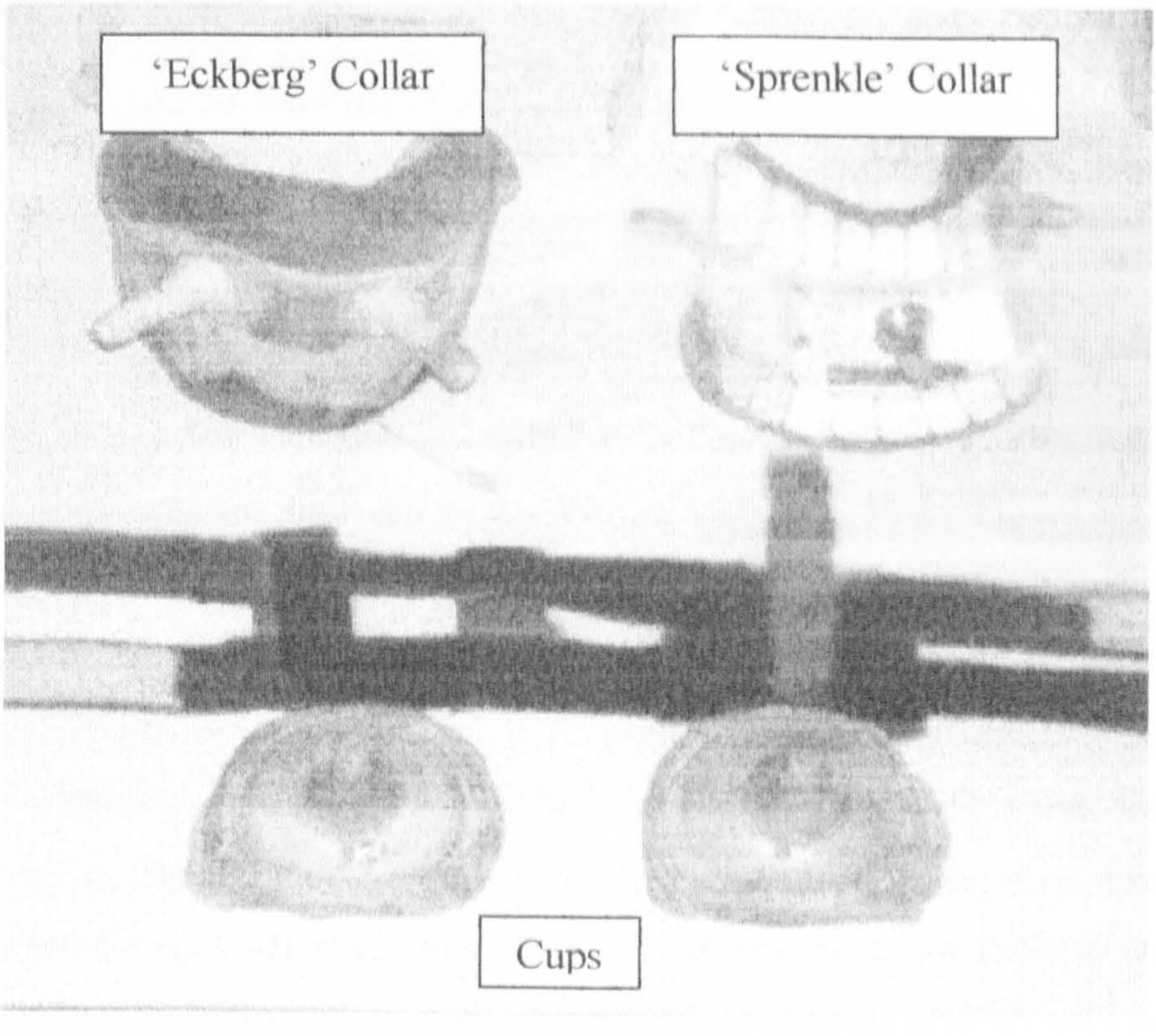


FIGURE O.2, NECK CUPS AND ECKBERG AND SPRENKLE COLLARS

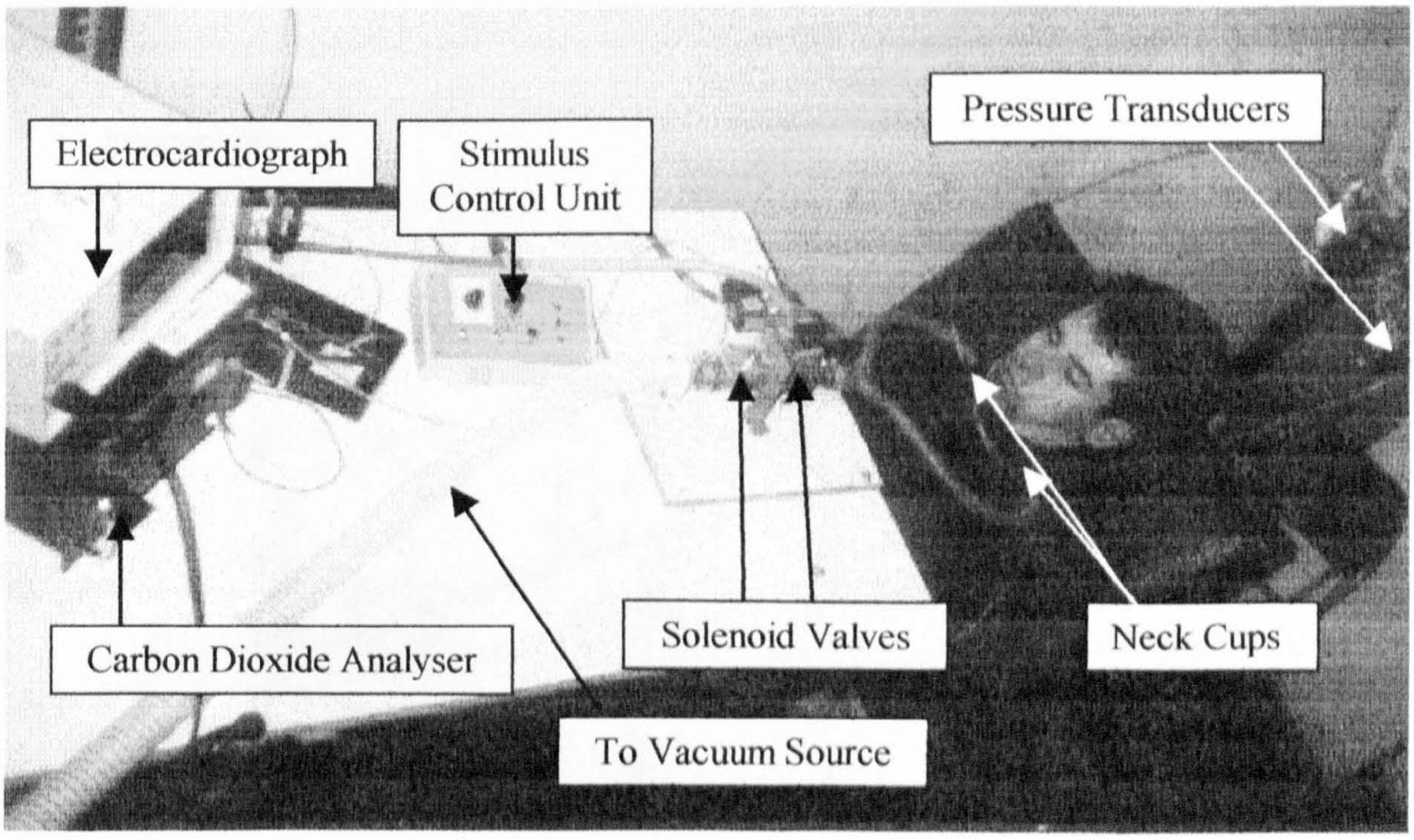


FIGURE O3, NECK CUPS AND CAROTID SINUS STIMULATION SYSTEM. The Cups were plastic half spheres with a small semi circular section cut away on one side and a slightly larger section cut away opposite the first. A 2 cm thick strip of blue-tac (Evostick, Staines) was placed around the rim of each cup to provide an airtight seal.

Responses to arterial pressure change level off and in some cases decrease over a threshold carotid sinus distending pressure in the region of 155 - 160 mmHg (Koch, 1931). This threshold corresponds to neck pressures of around -55 to –60 mmHg. Consequently, baroreflex gain was measured to be the steepest part of the relationship of R-R interval responses and neck pressures between –15 and –55 mmHg.

Statistical Analysis. Paired Student 'T' tests were used to examine differences between samples sizes equal or greater than eight involving only two groups. Single factor Analysis of Variance combined with Tukey's post hoc analysis of means was used for analysis involving sample sizes greater than eight for which there were three or more groups. Pearson Product Moment correlation coefficients were calculated to ascertain the degree of correlation between variables. A confidence interval of 0.05 was assumed for two tailed outcomes except where shown.

Results. The principle findings of the study are firstly that carotid sensitivity measured using neck Cups was not different to that measured by means of Sprenkle or Eckberg collars; and secondly that the reliability of the use of neck Cups was either greater (for

highly responsive subjects) or the same as (for poorly responsive subjects) that seen for the Sprenkle and Eckberg methods.

Table O.1 shows the grand mean gains derived from each collar device compared to that derived from Cups during the same experimental period. Each grand mean is the mean of the subject slopes calculated by plotting average responses against relative neck pressures. No significant differences were found between the mean baroreflex gains.

	Cup	Sprenkle	Cup	Eckberg
Mean	4.43	2.94	3.34	2.07
SE	± 1.71	± 2.17	± 2.92	± 2.08
ms.mmHg^{-1}				

TABLE O.1, MEAN GAINS DERIVED DURING 'CUPS vs ECKBERG' (n = 8) AND 'CUPS vs SPRENKLE' (n = 8) COMPARISONS

The relationships between change in R-R interval and neck pressure for each device can be seen in Fig O.4. All mean responses are plotted against respective neck pressures. Table O.2 lists the maximum slopes of the binomial regression lines derived from the analysis of all subject mean responses for a given device.

A comparison of absolute change in R-R interval produced by each method showed that the responses derived from the use of Cups were significantly greater than those derived from the Eckberg collar.

	Cup	Sprenkle	Eckberg
n =	12	8	8
Mean Gain	5.13	5.10	3.13
ms.mmHg^{-1}			

TABLE O.2, MEAN GAINS FOR NECK CUPS, ECKBERG AND SPRENKLE COLLARS

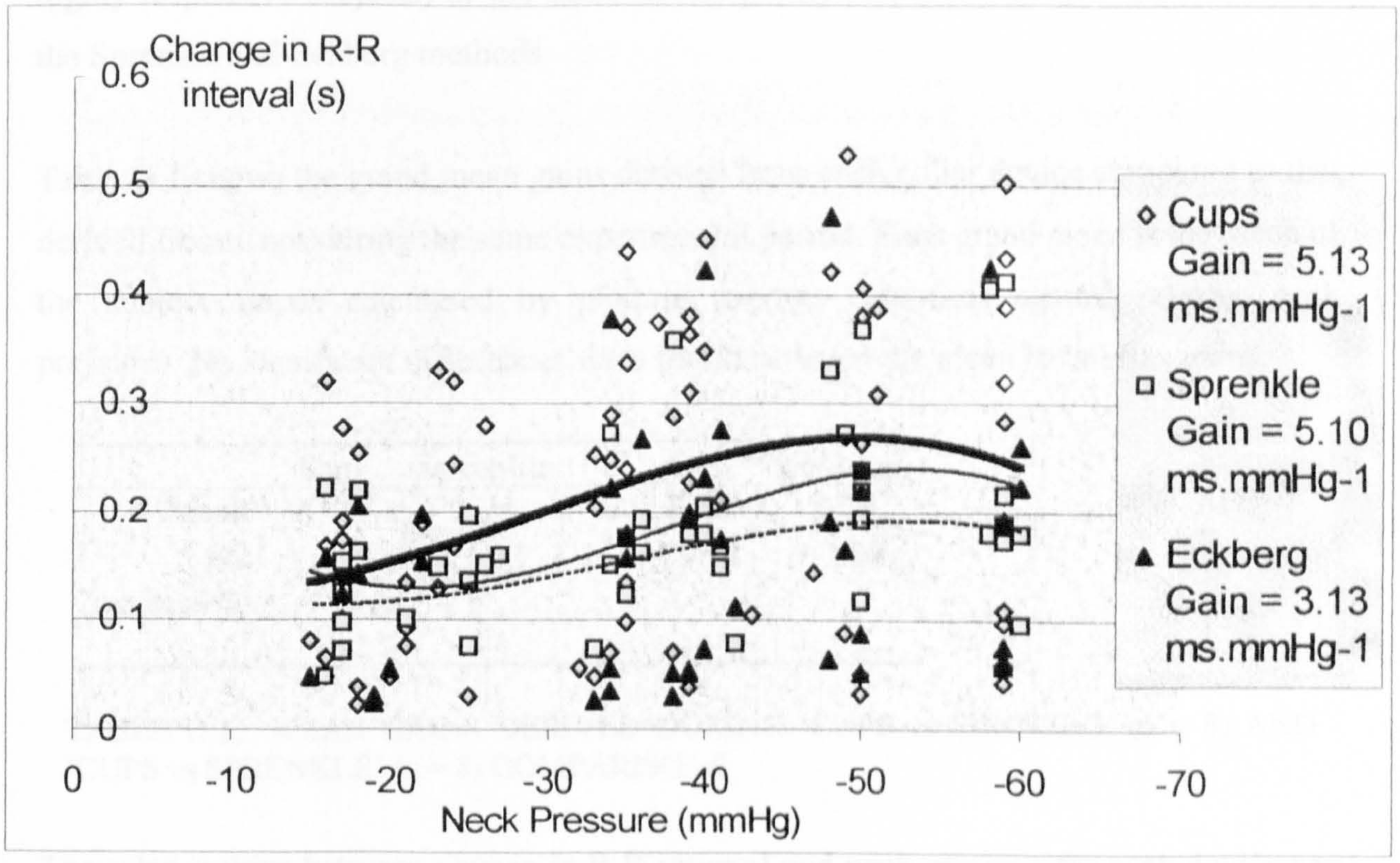


FIGURE O.4 MEAN CAROTID BAROREFLEX RELATIONSHIPS FOR THE ECKBERG (DASHED' LINE), SPRENKLE (SOLID LINE) AND CUPS (THICK LINE) METHODS. Each data point represents the mean response of one subject to corresponding neck pressure for one device. The slopes shown were derived from the binomial regression of all mean responses according to device.

Table O.3 shows the mean gains derived from Cups, Sprenkle and Eckberg device for the four subjects who undertook measurements using all methods. Statistical analysis was not undertaken due to the small sample size; however, baroreflex slopes were found to be of the same magnitude as those of the primary comparisons. The individual gains for the Cups tended to be greater than those of the collar methods, as shown by the group means in Table O.3.

	Cup	**Sprenkle**	**Eckberg**
Mean	3.6	2.3	2.68
SE	± 2.33	± 2.46	± 2.85

$ms.mmHg^{-1}$

TABLE O.3 MEAN GAINS DERIVED FROM CUPS, ECKBERG AND SPRENKLE DEVICES (n = 4)

Table O.4 lists the mean gains measured on four occasions for each device for two subjects. Subject LM was a high responder showing large changes in R-R interval for given neck pressures, whereas subject SE was a low responder for which small changes in R-R interval were elicited form given neck pressures. The Cups mean gains were greater than those produced by either collar device.

	Cup	**Sprenkle**	**Eckberg**
		($ms.mmHg^{-1}$)	
Subject LM			
Train 1	6.8	5.5	6.8
Train 2	9.6	8.9	10.7
Train 3	6.7	4.7	8.7
Train 4	4.6	4.1	1.1
Mean	**6.93**	**5.80**	**6.83**
SE	**± 2.05**	**± 2.14**	**± 4.14**
Subject SE			
Train 1	1	0.9	0.3
Train 2	1.8	2.3	0.5
Train 3	0.8	0.3	0.4
Train 4	2.8	0.1	0.4
Mean	**1.60**	**0.90**	**0.40**
SE	**± 0.91**	**± 0.99**	**± 0.08**

TABLE O.4 GAINS DERIVED FROM TWO SUBJECTS FOR FOUR TRAINS OF PRESSURES USING CUPS, ECKBERG AND SPRENKLE DEVICES

Table O.5 shows the strengths of relationships between the responses derived from each train of pressures i.e. trains 1, 2, 3 and 4, for each device for the two subjects. For subject LM all relationships between the Cups responses were highly significant ($p < 0.01$), whereas only 1 and 3 relationships were significant for Eckberg and Sprenkle methods respectively. For subject SE only 1 significant relationship was found between responses for each method.

SUBJECT LM

Cups

Train	*1*	*2*	*3*
2	**0.926**		
3	**0.917**	**0.950**	
4	**0.928**	**0.940**	**0.996**

Eckberg

Train	*1*	*2*	*3*
2	0.367		
3	**0.831**	0.585	
4	0.664	0.401	**0.874**

Sprenkle

Train	*1*	*2*	*3*
2	**0.780**		
3	0.535	0.479	
4	**0.807**	**0.997**	0.483

SUBJECT SE

Cups

Train	*1*	*2*	*3*
2	0.394		
3	0.496	0.391	
4	0.700	**0.900**	0.538

Eckberg

Train	*1*	*2*	*3*
2	0.622		
3	0.343	0.620	
4	**0.882**	0.320	0.621

Sprenkle

Train	*1*	*2*	*3*
2	-0.721		
3	0.058	-0.011	
4	**0.941**	-0.547	0.401

Bold = $P < 0.05$, **Bold** = $P < 0.01$

TABLE O.5, PEARSON CORRELATION COEFFICIENTS FOR THE RESPONSES OF FOUR TRAINS OF PRESSURES FOR TWO SUBJECTS. Values show the strength of relationship between the responses measured during two different applications of neck suction.

Figs O5, O6 and O7 show mean responses from the 4 trains of pressure plotted against neck pressure for subjects LM and SE for the Cups, Sprenkle and Eckberg devices respectively.

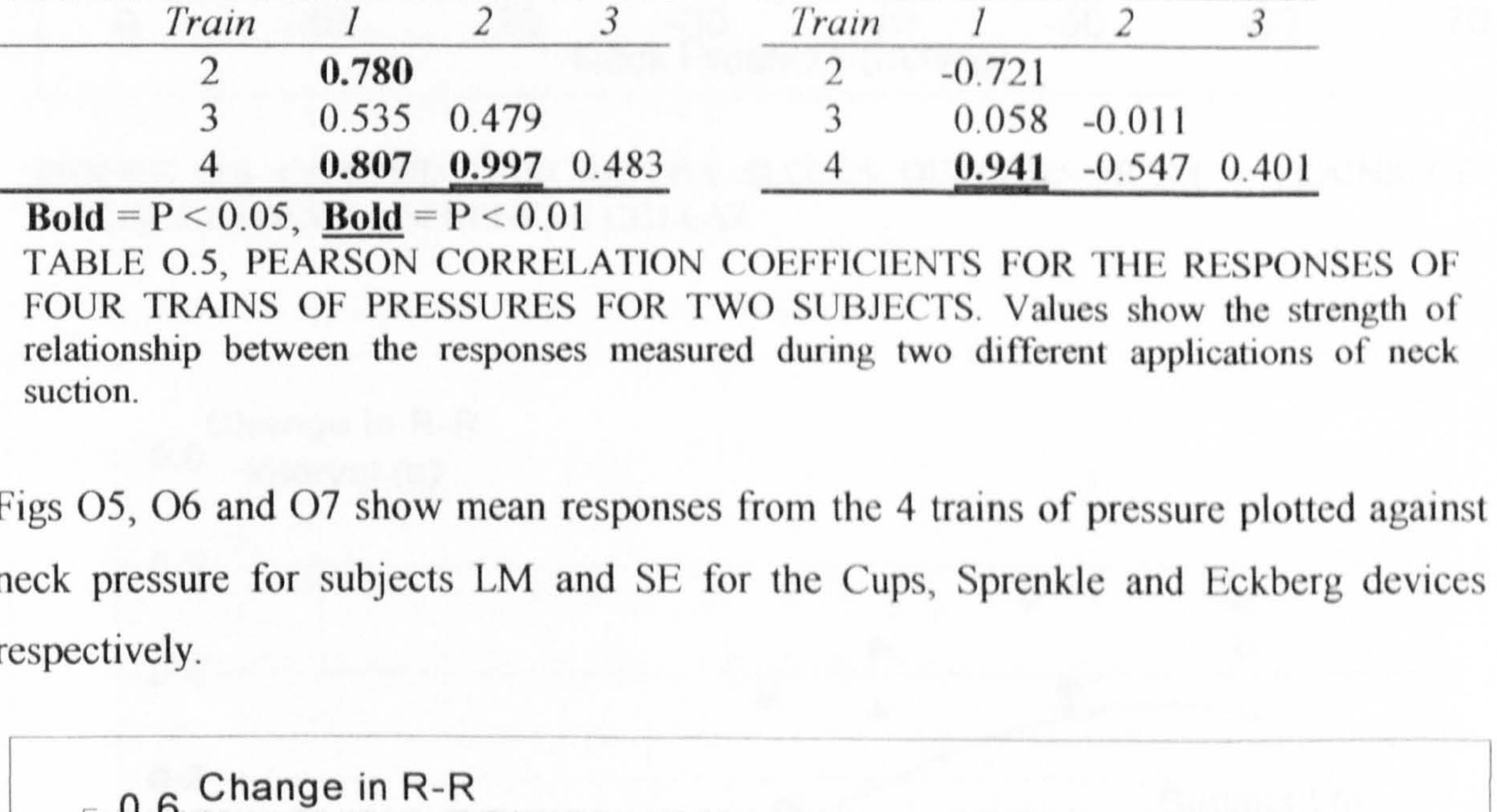


FIGURE O.5 CAROTID BAROREFLEX SLOPES DERIVED FROM 4 TRAINS OF PRESSURES USING NECK CUPS

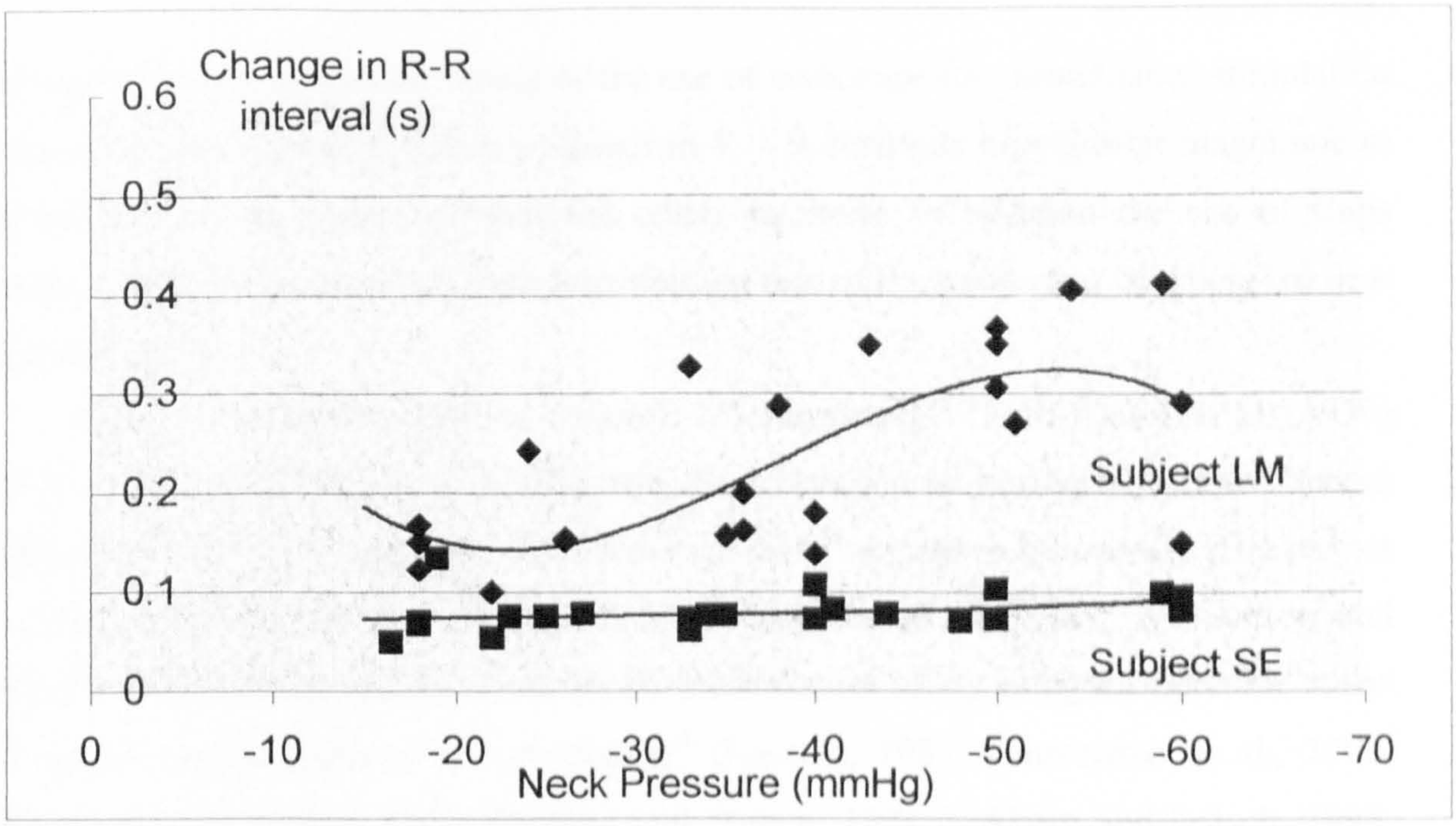


FIGURE O.6 CAROTID BAROREFLEX SLOPES DERIVED FROM 4 TRAINS OF PRESSURE USING A SPRENKLE COLLAR

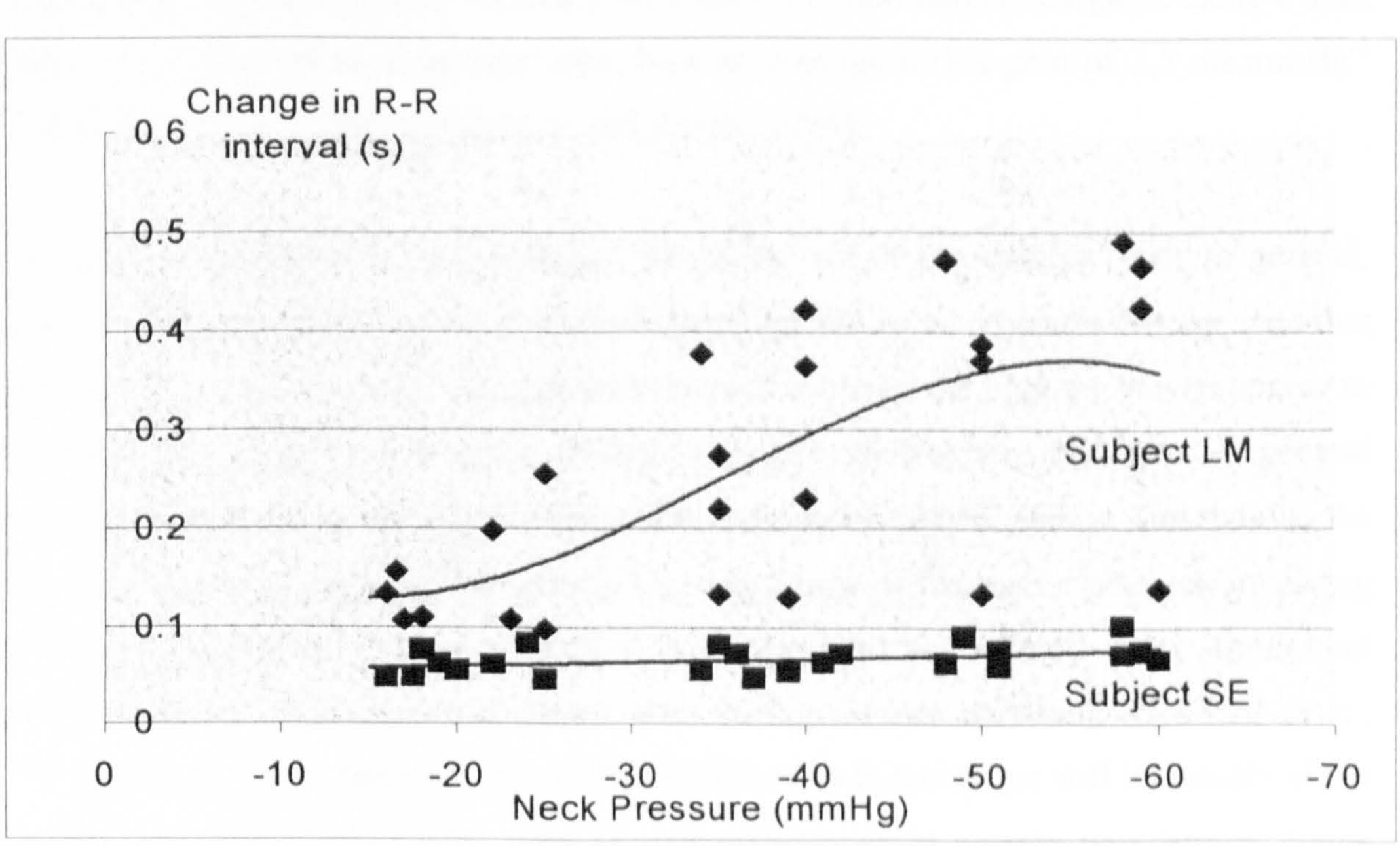


FIGURE O.7 CAROTID BAROREFLEX SLOPES DERIVED FROM 4 TRAINS OF PRESSURES USING AN ECKBERG COLLAR

DISCUSSION

The results of this preliminary study of the use of neck cups for carotid sinus stimulation indicate that the method produces changes in R – R intervals of a similar magnitude to that elicited by the more conventional collar methods. In addition the use of Cups appears as reliable or possibly more reliable than that of the traditional (Eckberg) or new (Sprenkle) collars.

Carotid baroreflex gains of between 2.0 ms.mmHg^{-1} (Tafil-Klawe et al., 1990) and 12.0 ms.mmHg^{-1} (Shi et al., 1993b) have been reported for normal fit, healthy human subjects. Values in the region of 4.0 – 8.0 ms.mmHg^{-1} appear to be average (Eckberg et al., 1975; Eckberg, 1976; Eckberg, 1977b; Convertino et al., 1989; Williamson and Raven, 1994). An examination of the results from studies solely using the Sprenkle collar reveals an average gain of 6.0 ms.mmHg^{-1} (Kasting, 1987; Convertino et al., 1989; Ludwig and Convertino, 1991; Eckberg and Fritsch, 1992; Eckberg and Fritsch, 1993; Shi et al., 1993b). Those studies employing the Eckberg collar produce an average of 5.4 ms.mmHg^{-1} (Eckberg et al., 1975; Eckberg, 1976; Eckberg, 1977b; Ebert et al., 1984; Barney et al., 1988), whereas studies which have reported baroreflex gains using a split collar or two individual chambers/cups show an average reflex gain of 3.5 ms.mmHg^{-1} (Tafil-Klawe et al., 1990; Williamson and Raven, 1994).

The mean slopes derived in this study, therefore, are of the correct order in general, however, with regard to individual devices, the Cups produced a greater average gain that that reported in the literature using similar devices, whereas the Eckberg results appear to be lower than those seen in other studies. Although the Eckberg principles in general have been adhered to by the investigators mentioned above and in this study, the apparatus and exact details of the protocols vary. Some of the earlier research involving the Eckberg collar used relatively long stimuli durations and in most cases stimulation occurred during held expiration rather than during normal breathing (Eckberg et al., 1975; Eckberg, 1976; Barney et al., 1988). Differences in technique will inevitably effect the measurement of baroreflex gain as will differences in sample populations. Some differences in results between those of this study and other research, therefore, will be due to variations in methodology. What is of note, however, is that the results from the Eckberg collar for this study do appear substantially lower than those reported by other researchers. It is possible that the collar used in this instance was not as effective at

transmitting pressure as those used in other studies, or that the combination of the protocol, apparatus and collar used was not optimal in this case. The results for the Sprenkle collar appear close to expected values and thus suggest that the device was used appropriately. The finding that the values of the baroreflex gains derived from the Cups were not only on a par with other devices, but better than those reported by studies using a split technique, indicate that the apparatus and protocol combined with the Cups used for this study was effective. This view is supported by the significantly greater responses produced by the Cups than the Eckberg collar, although as discussed it is accepted that the Eckberg responses could have been sub-optimal.

An examination of the relationships between the gains elicited from the three devices reveals significant correlations between the Eckberg and Cups results ($r = 0.66$) and the Sprenkle and Cups results ($r = 0.71$), but interestingly not between the two collars devices ($r = 0.28$). These results when considered with those of the strength of relationships derived for subjects LM and SE indicate a moderately high level of reliability for the Cups method, an intermediate level for Sprenkle and low reliability for the Eckberg. These data further indicate that either the Eckberg collar per se or its use with the apparatus and protocol in this study did not produce optimal or reliable responses.

The qualitative difficulties found during the study were that the height of the lead collar tended to hyper-extend the necks of the smaller subjects which may have had a bearing on carotid sinus responses. This problem, however, has not been reported in the literature and only occurred in the case of two subjects for this study. Furthermore, the amount of dead space in the Eckberg collar was sufficiently large that it was necessary to fill the internal space with plasticine to achieve an adequate rate of pressure application. Although great care was taken to ensure that the filling did not affect pressure application to the area of the carotid sinus, filling in this manner may have changed the specifications of the collar i.e. it was heavier and possibly less compliant which could have altered its effectiveness.

The neck Cups used were small, medium or large according to subject fit. This degree of individual fitting may have provided a small advantage of this method over that of the collars for which only one size has been proposed (Eckberg) or for which only one size

was available (Sprenkle). The Sprenkle collar is also manufactured in three sizes, small, medium and large, however, details of the size of the collar used in the present study were not available and other sizes could not be obtained. Consequently, subjects were not recruited for whom the collar did not fit. The fact that small and medium height/weight subjects were suitable suggests that the collar was a medium, however, the possibility exists that in some cases a Sprenkle collar of another size may have produced greater responses.

In conclusion, the results of this study indicate that the use of neck Cups in combination with the apparatus and protocol outlined in the main text of this study, was appropriate for the stimulation of the carotid sinus to derive a measure of carotid baroreflex function.

APPENDIX P

PRELIMINARY INVESTIGATIONS OF ELEMENTS OF THE CARDIOPULMONARY BARORECEPTOR ASSESSMENT EQUIPMENT.

Preliminary investigations were performed to ascertain the validity of using mild LBNP (20 mmHg or less) to decrease central blood volume without affecting arterial pressure and to examine the reliability of forearm plethysmography for measuring forearm blood flow.

The Effect Of –20 mmHg Lower Body Negative Pressure Upon Arterial Pressure.

The objective was to ascertain whether mild LBNP (-20 mmHg) significantly affected arterial pressure. Five subjects were exposed to 20 mmHg of LBNP on between 1 and 3 occasions. Electrocardiogram was recorded using lead II of a 3 lead configuration and arterial pressure was measured by means of Finapres. Arterial pressure was recorded for 10 min before, during and 10 min after the application of LBNP. LBNP was applied for 2 min. Mean systolic and diastolic arterial pressure measurements were obtained from 24 s sections of pressure recordings. The pressures measured at ambient chamber pressure within 60 s of the start of LBNP and those measured 20 – 60 s after the initiation of LBNP (Early LBNP) were used for comparison as were those recorded 80 – 120 s after the initiation of LBNP (Late LBNP) and those measured at ambient 60 s after cessation of chamber negative pressure.

Results. A single factor ANOVA revealed no significant differences ($p > 0.05$) between ambient systolic, diastolic or pulse pressures and those measured during LBNP (Table P.1). The strength of relationship between ambient and LBNP arterial pressures measurements (Fig P.1) was examined using Pearson's Product Moment and showed a highly significant correlation ($r = 0.98$, $df = 49$, $p < 0.01$)(Fig P.1).

TABLE P.1 ARTERIAL PRESSURE MEASUREMENTS AT 0 AND 20 mmHg LOWER BODY NEGATIVE PRESSURE (n = 5).

Mean ± SE	**Ambient**	**LBNP Early**	**LBNP Late**	**Ambient**
Systolic Pressure	124.2 ± 15	121.8 ± 17.1	122.7 ± 15.7	122.3 ± 17.1
Diastolic Pressure	74.5 ± 13.3	73.8 ± 16.4	75.7 ± 13.9	75.9 ± 13.8
Pulse Pressure	49.7 ± 8.5	48.0 ± 9.3	47.0 ± 9.6	46.4 ± 17.4

LBNP Early = Measures taken between 20 and 60 s of the start of LBNP.
LBNP Late = Measures taken between 80 and 120 s of the start of LBNP.

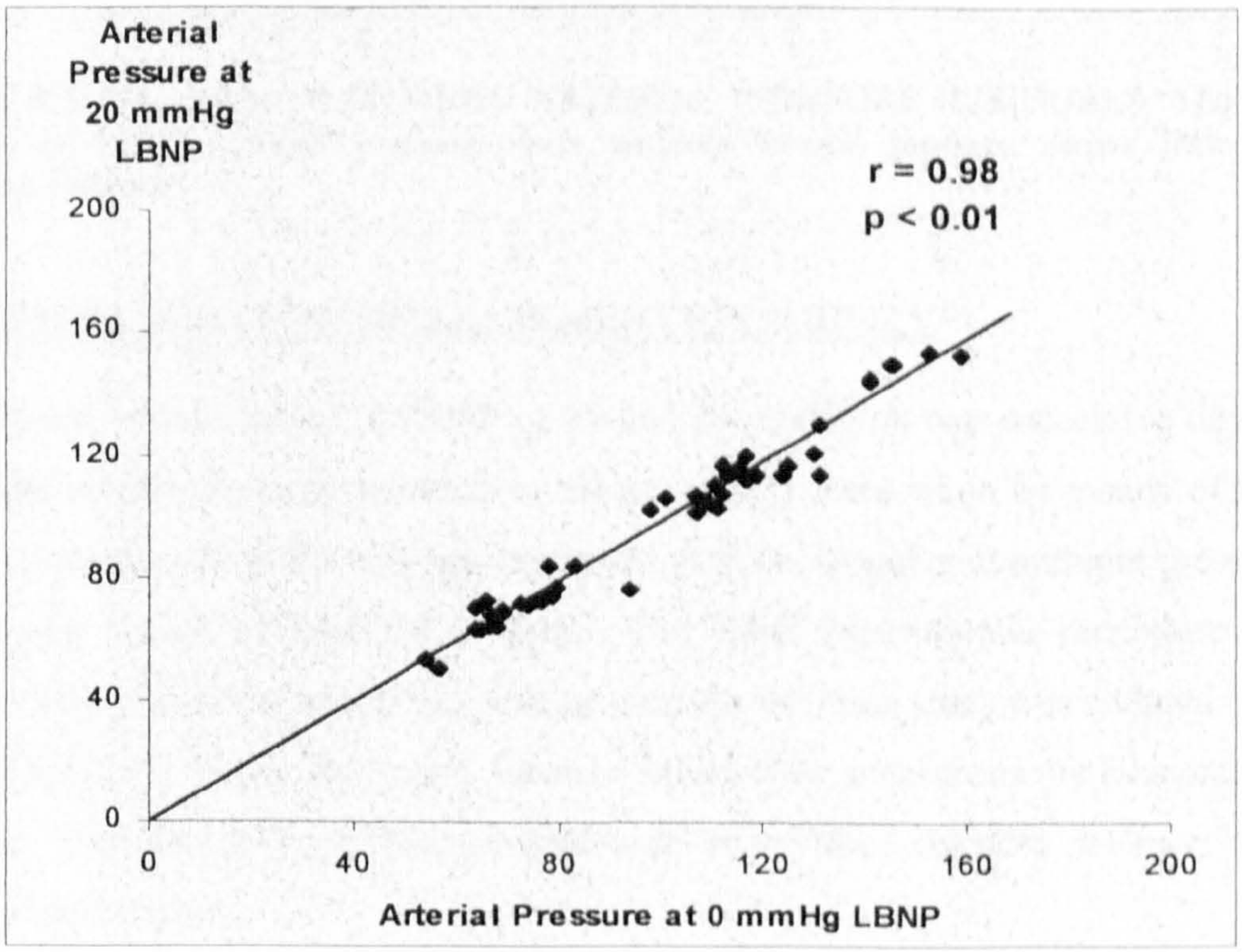


FIGURE P.1, RELATIONSHIP OF MEAN ARTERIAL PRESSURE MEASURED AT 0 AND 20 mmHg LOWER BODY NEGATIVE PRESSURE. Figure P1 shows the regression of mean systolic and diastolic arterial pressure for LBNP against those measured at ambient chamber pressure. Each data point is the mean systolic or diastolic arterial pressure for one experimental period for one subject.

An examination of the residuals plot of LBNP arterial pressure on ambient shows the LBNP arterial pressure variance from mean was within ± 10 mmHg with the exception of two outlying values which were within ± 20 mmHg and showed no clear systematic variance.

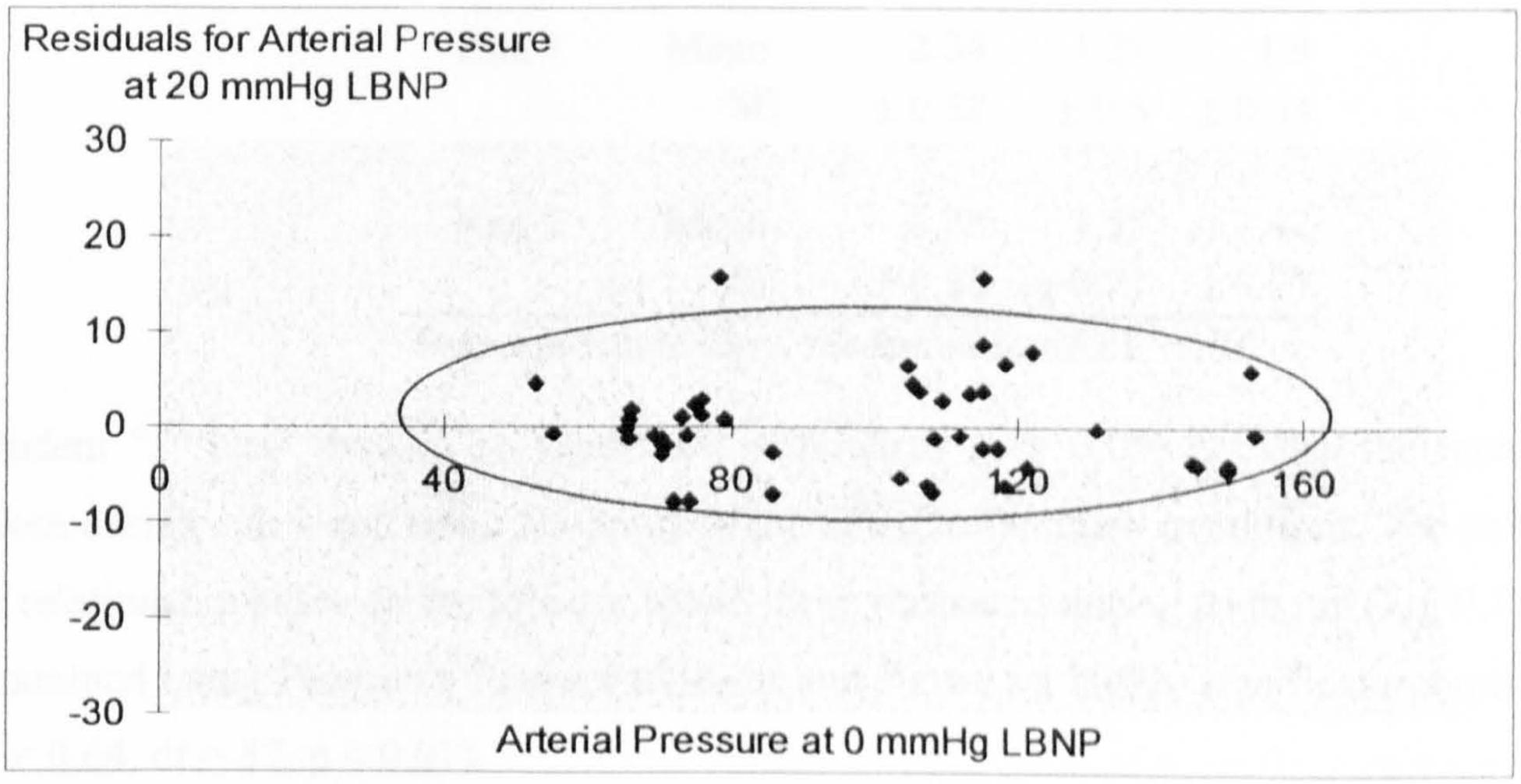


FIGURE P.3. 20 mmHg LBNP MEAN ARTERIAL PRESSURE RESIDUALS. The residuals of LBNP arterial pressure upon ambient arterial pressure shows little systematic variance.

FOREARM BLOOD FLOW MEASUREMENT RELIABILITY

Five subjects were exposed to LBNP of 15 and 20 mmHg on two successive days at the same time of day. Forearm blood flow measurements were taken by means of forearm plethysmography whilst the subjects lay at rest with the chamber at ambient pressure and during each period of negative pressure. The same experimental procedure for the measurement of forearm blood flow as that used for the main study was adopted.

Table P.2 shows the mean forearm blood flow measurements (the mean of 3 measures from each subject) derived from each of the three chamber pressures for both experimental sessions.

TABLE P.2 MEAN FOREARM BLOOD FLOW MEASUREMENTS AT AMBIENT PRESSURE AND LBNP

		Chamber Pressure, mmHg		
		0	-15	-20
Run 1	Mean	2.34	1.29	1.4
	SE	± 0.58	± 0.5	± 0.54
Run 2	Mean	2.24	1.55	1.42
	SE	± 0.28	± 0.71	± 0.21

Forearm Blood Flow measured in $ml.dl^{-1}.min^{-1}$.

Student 'T' tests showed no significant differences ($p > 0.05$) between the measures taken during run 1 and run 2 for either of the LBNP or ambient conditions. The strength of relationship between the forearm blood flows measured during each run (Fig P.3) was examined using Pearson's Product Moment and showed a highly significant correlation ($r = 0.64$, $df = 57$, $p < 0.01$).

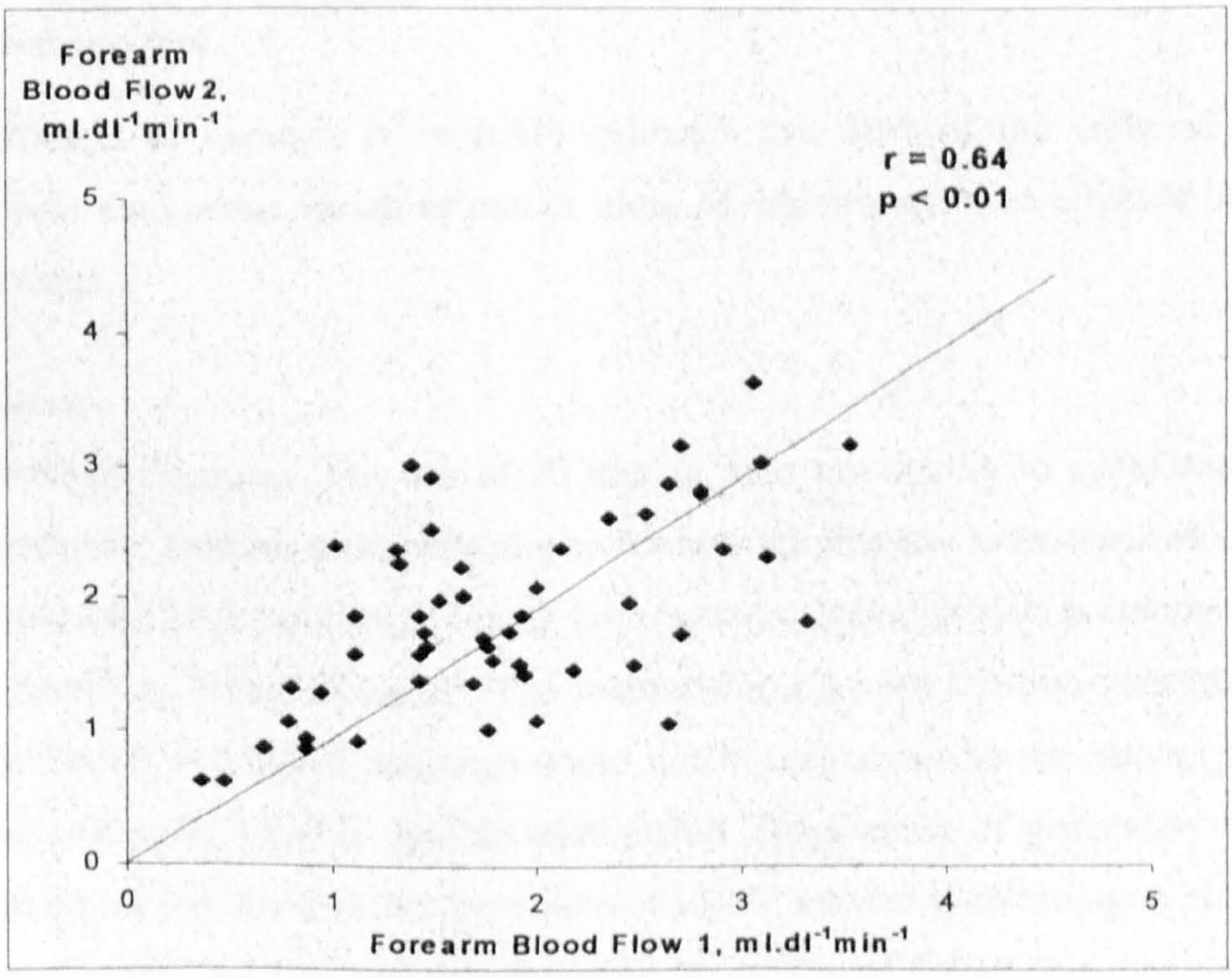


FIGURE P.3 THE REGRESSION OF TWO SUCCESSIVE (SEPARATE DAYS) FOREARM BLOOD FLOW MEASUREMENTS DURING 15 OR 20 MMHG LBNP. Each data point shows the relationship between two individual blood flows e.g. first blood flow measured at -15mmHg during day 1 against first flow measured at –15 mmHg for day two.

An examination of the residuals plot of the forearm blood flow residuals for run 1 against blood flow measures for run 2 showed a reasonable scatter, however, a slight inclination

is apparent indicating the possibility of a small effect of extraneous variables upon blood flow measurements. The effect shows slightly greater run 1 residuals for lower blood flows (LBNP) and slightly lower residuals for higher blood flows (ambient).

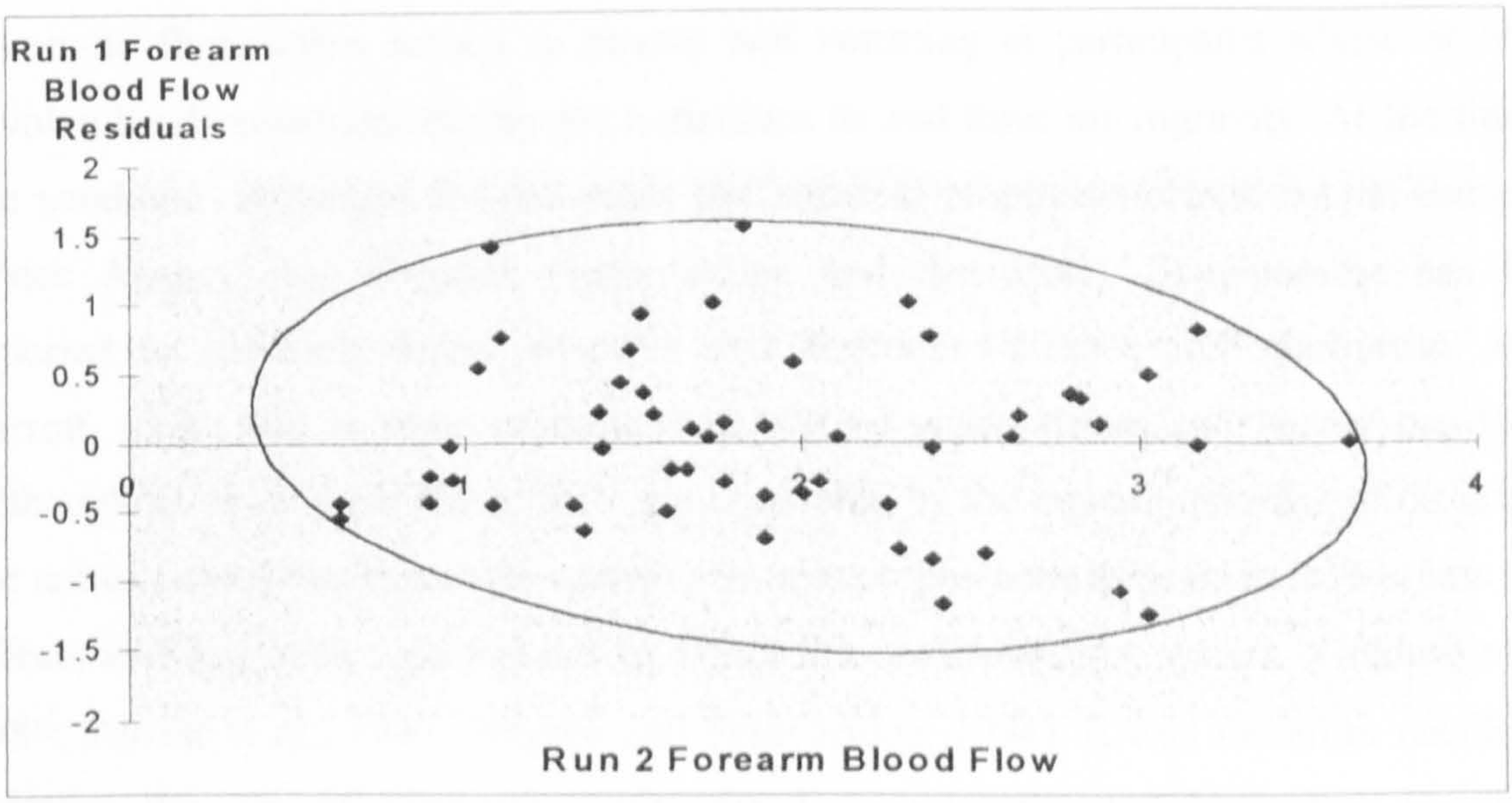


FIGURE P.4. 20 mmHg LBNP FOREARM BLOOD FLOW RESIDUALS. The residual plot of forearm blood flow measurements of run 1 against those of run 2 indicate the possibility of the systematic influence of extraneous variables upon the measurements of one or other of the experimental measures.

The coefficient of variance ($r^2 = 0.41$) indicates that 59% of the variance shown is derived from extraneous variables one or more of which may have effected blood flow measurements.

Conclusions.

Arterial Pressure. The use of 20 mmHg does not appear to significantly affect arterial pressure. Despite a slight tendency for arterial pressure to be reduced during the first minute of LBNP (not significant) both systolic and diastolic pressures return to ambient levels by 2 min of LBNP. The relationship between the two measures is such that only 4% ($r^2 = 0.96$) of variance could not be explained by the two experimental conditions indicating a highly reliable relationship. The absence of systematic variance in the residual plot implies that the regression of LBNP arterial pressure upon ambient was a suitably accurate analysis and that therefore 20 mmHg of LBNP does not significantly affect arterial pressure measured by Finapres.

Forearm Blood Flow. Reliability of forearm plethysmography for the measurement of forearm blood flow was high, however, the greater degree of influence of extraneous variables as shown by the coefficient of determination and the residuals plot shows that experimental conditions must be closely controlled.

APPENDIX Q

ASSESSMENT OF THE EFFECTS OF CINNARIZINE UPON INTEGRATED BAROREFLEX SENSITIVITY

Parabolic flight often results in nausea and vomiting in participants whose activities involve head movement during the transitions to and from microgravity. At the time of the parabolic campaigns for this study the standard prophylactic used by the European Space Agency was Scopdex (scopolamine and dexadrine). Scopolamine has been reported to adversely affect attention and alertness (Wesnes and Warburton, 1983; Parrott, 1986) and in some cases lead to blurred vision (Innes and Nickerson, 1975). Although some of these side-effects are countered by the concomitant use of dexadrine, the use of cinnarizine as an anti-motion sickness prophylactic appears to lead to less side-effects and has been reported not to affect the cardiovascular system (Golding et al., 1989; Parrott et al., 1990; Pingree and Pethybridge, 1994). It was therefore decided to examine the use of cinnarizine (Stugeron) during integrated baroreflex sensitivity measurement.

Cinnarizine. The results of a comparison of a number of anti-motion sickness prophylactics undertaken by Parratt and Wesnes (1987) showed that both 0.6 mg scopolamine and 30 mg cinnarizine significantly affected cognitive function and alertness (Parrott and Wesnes, 1987), findings in agreement to those of Pingree and Pethybridge (1994), but who reported that cinnarizine produced less drowsiness than scopolamine. Golding et al (1989) in a comprehensive examination of the effects of cinnarizine and hyoscine[28] found that of 13 indices of cognitive, physiological and motor function, hyoscine significantly affected 6 and 30mg oral cinnarizine affected only 1. The index affected by cinnarizine was that of reaction time which produced a 10% impairment for 3 of 12 subjects, 5 to 7 hours post ingestion.

Despite observations that cinnarizine affects cognitive function, doses of between 30 and 75 mg have been reported to produce no significant effect on heart rate (Golding et al., 1989; Parrott et al., 1990) or blood pressure (Schuermans et al., 1971). The number of studies examining the cardiovascular effects of cinnarizine, however, is few and thus a preliminary assessment of the effects of cinnarizine upon integrated baroreceptor sensitivity was undertaken for this study to determine whether any effect upon baroreceptor sensitivity index (BRSI) measurement would result.

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[28] Another commonly used anti motion sickness drug.

METHOD

Signed informed consent to participate in a study of the effects of cinnarizine upon the baroreflex response to Valsalva's manoeuvre was obtained from three male and three female subjects (mean age 28.2 ± 5.91 yr). A double blind design incorporating a placebo was used. Subjects were required to undertake two sets of Valsalva's manoeuvres, one after taking 30 mg cinnarizine and the other after taking 30 mg placebo (vitamin pills). The sets of manoeuvres were performed at the same time of day on different days in a climatic chamber (21° C and 50% humidity). The subject was asked to take cinnarizine or placebo 3 hr before the Valsalva's manoeuvres were to be performed to ensure that they were performed whilst under the influence of cinnarizine. The tablets were taken with orange juice to disguise the taste and with the eyes closed to prevent recognition.

The apparatus consisted of a mouthpiece connected by fine bore tubing to a pressure transducer (Gould Statham PD23, Ilford) and mercury manometer (Fig R.1). A small leak was included in the mouthpiece assembly to prevent closure of the glottis during the expiratory effort. The pressure transducer was connected to a Maclab amplifier and 4/e processor (AD Instruments, Hastings) which in turn was connected to a PowerMac 5200 computer. The subject could see the mercury column when performing the manoeuvre thus enabling the correct expiratory effort to be maintained.

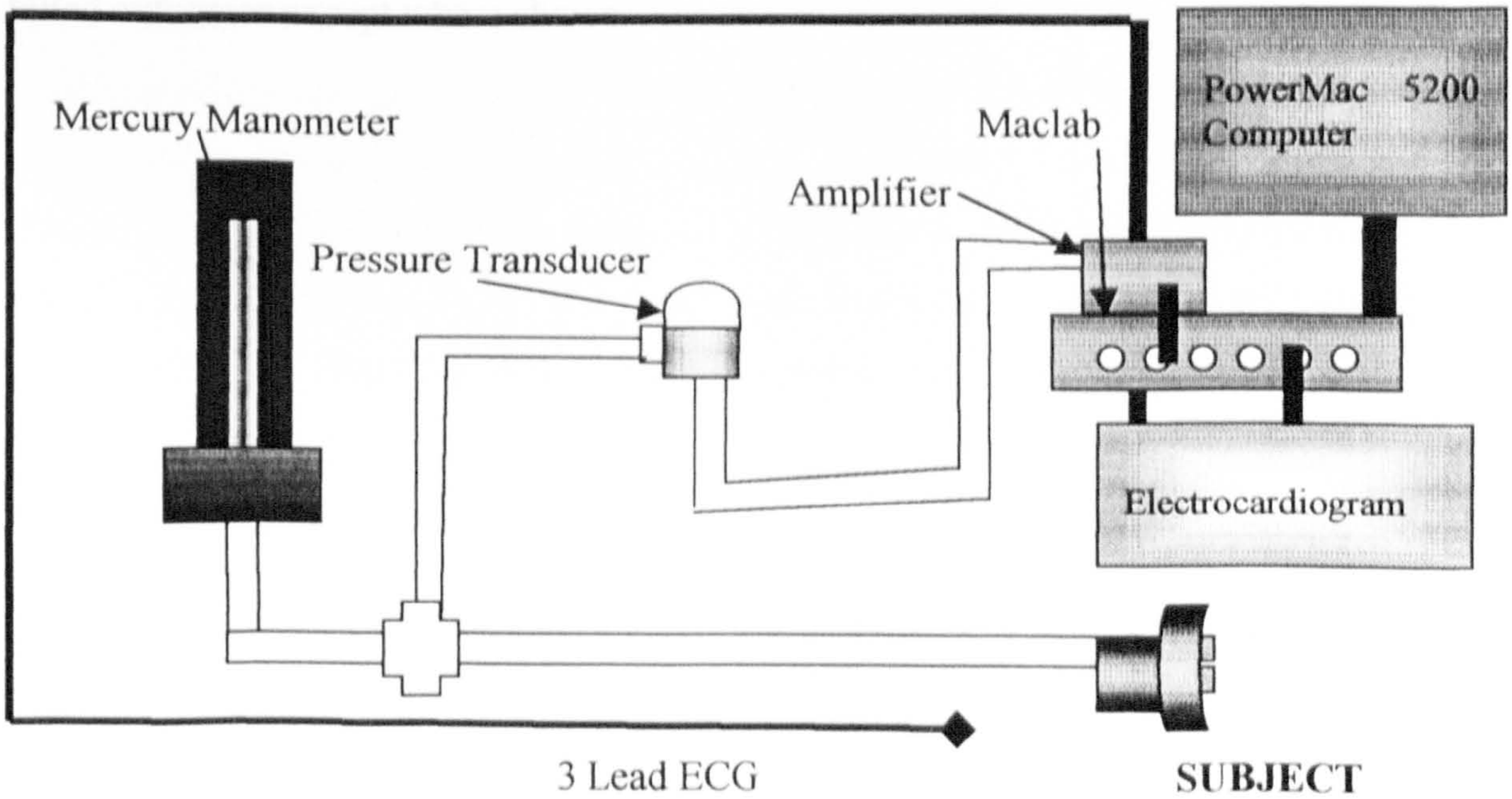

FIGURE R.1 APPARATUS FOR THE MEASUREMENT AND RECORDING OF RESPONSES TO VALSALVA'S MANOEUVRE

Three hours after ingesting the tablets the subject came to the climatic chamber and had a 3 lead electrocardiograph and Finapres attached for R –R interval and non-invasive arterial pressure measurement respectively. The subject was then instructed to practice a standardised Valsalva's manoeuvre (expiratory effort of 40 mmHg for 10 s after a deep inspiration) until he/she was able to maintain a consistent 40 mmHg (± 1 mmHg) for 10 s. The subsequent experiment consisted of 3 Valsalva's manoeuvre whilst seated, leg outstretched and 3 manoeuvres whilst at 6° head-down tilt. At least 2 min was allowed between each manoeuvre. Arterial and mouth pressures and ECG were recorded throughout. Baroreceptor sensitivity was measured by means of the relationship calculated between R-R interval and systolic pressure during phase IV of the Valsalva's manoeuvre, as used in the main study.

Statistical Analysis. Wilcoxon tests of ranks were used to examine the differences between groups of data numbering less than 8. Paired Student 'T' tests were used to examine differences between samples sizes equal or greater than 8 involving two groups. Single factor Analysis of Variance combined with Tukey's post hoc analysis of means was used for analysis involving sample sizes greater than 8 for which there were three or more groups. Pearson Product Moment Correlations were performed to ascertain the degree of correlation between variables. A confidence interval of 0.05 was assumed for two tailed outcomes except where shown.

RESULTS

Table R.1 lists the mean BRSI values measured in each posture after ingestion of cinnarizine and placebo. No significant difference in means ($p > 0.05$) existed between the placebo and test conditions for head-down tilt, seated or for the combination of the two postures.

	BRSI ($ms.mmHg^{-1}$) Mean ± SE, n = 6	
Posture	**Cinnarizine**	**Placebo**
Head-down tilt	21.55 ± 7.88	24.72 ± 7.75
Seated	21.88 ± 12.75	19.34 ± 8.27
Combined Mean	21.71 ± 10.1	22.03 ± 8.14

TABLE R.1 BARORECEPTOR SENSITIVITY INDEX DERIVED FROM VALSALVA'S MANOEUVRE AFTER INGESTION OF CINNARIZINE OR PLACEBO (n = 6). Each value is the mean of the slopes derived from phase IV of the responses to 3 Valsalva's manoeuvres.

The strength of relationships between values derived under the influence of cinnarizine and those measured after placebo proved highly significant ($p < 0.01$) for the seated, head-down tilt and combined means when all BRSI values were considered ($r = 0.67$, 0.8 and 0.77 respectively, Fig R.2). The results of this brief study therefore show no significant effect of cinnarizine upon baroreflex responses to Valsalva's manoeuvre.

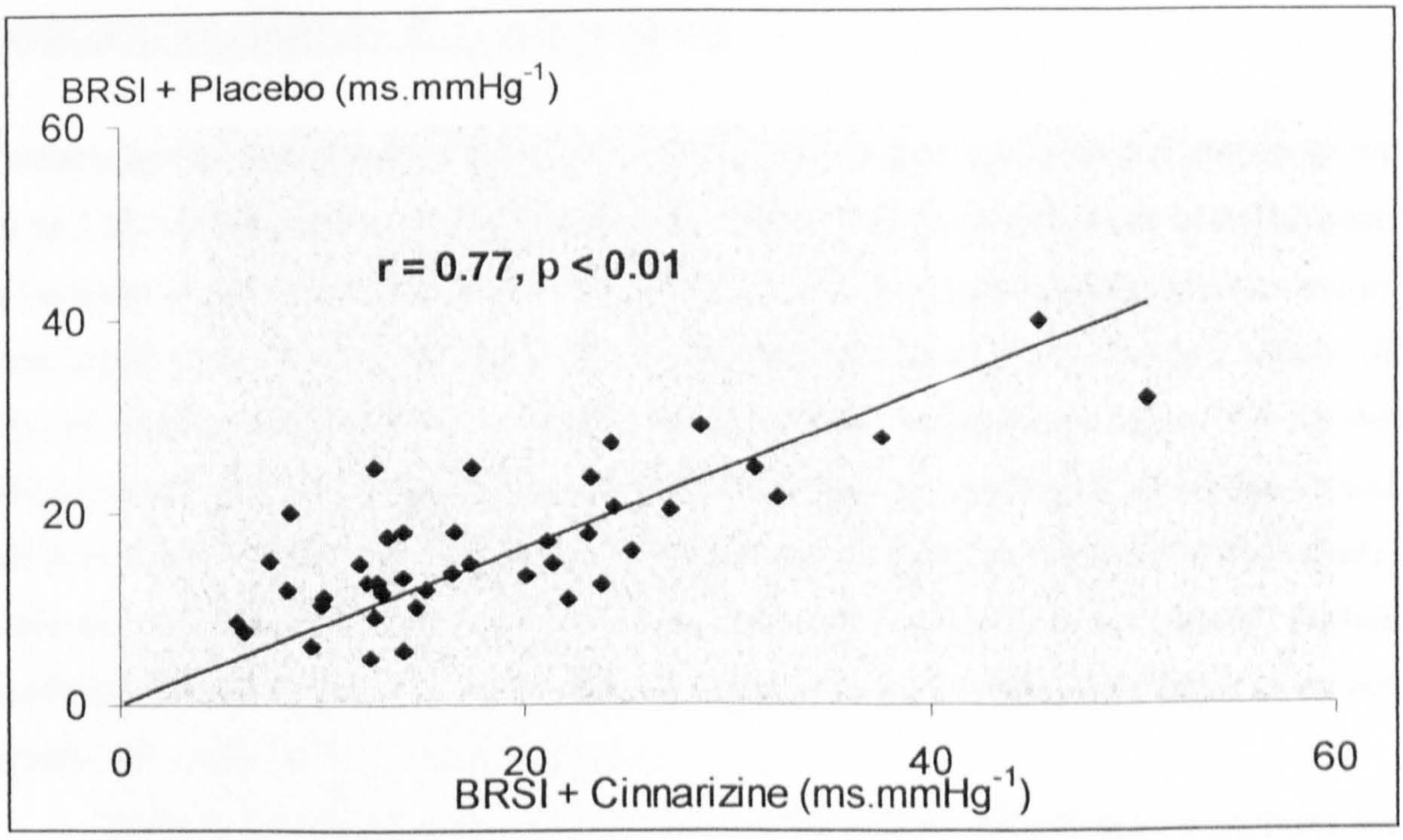

FIGURE R.1. RELATIONSHIP BETWEEN BARORECEPTOR SENSITIVITY INDICES MEASURED UNDER THE INFLUENCE OF 30 mg CINNARIZINE OR PLACEBO (n = 6). During each measurement session Valsalva's manoeuvres were performed in groups of three. The lowest BRSI derived under the influence of cinnarizine was paired with the lowest measured after placebo for the same position for each subject. Similarly the second lowest and highest BRSI values were paired. Each data point is therefore derived from matched pairs of BRSIs measured either at head-down tilt or when seated.

POST-HOC CONFIRMATION OF THE EFFECTS OF CINNARIZINE UPON INTEGRATED BAROREFLEX SENSITIVITY

Cinnarizine has been found to be effective from 1 to 3 hr post ingestion and remain so for up to 7 hr (Golding et al., 1989; Parrott et al., 1990). The plasma half-life of cinnarizine is between 3 and 5 hr (Morrison et al., 1979). As the pre-flight baseline measurements were conducted 1 to 2 hr before take-off, post-flight measures were obtained within 10 min of landing and flying time was 3 hr, all measurements were taken during the effective time period of Cinnarizine. Any potential effect of cinnarizine, therefore, would not prove problematic with regards to longitudinal comparisons required of this study, however, to facilitate inter-study or cross sectional comparison of results further confirmation that the use of cinnarizine as a prophylactic for parabolic flight does not significantly effect BRSI was undertaken.

Table R.2 shows the mean BRSI values for head-down tilt and seated postures for 3 subjects. Baseline (placebo) baroreflex sensitivity was measured under the same controlled conditions using the same experimental protocol as previously described. The results were compared to those measured in Bordeaux prior to parabolic flight, approximately 2 – 3 hr after ingestion of 30 mg cinnarizine. The baseline manoeuvres were performed in London and were conducted during early morning to correspond with the timing of the measures taken in France.

		BRSI ($ms.mmHg^{-1}$)	
Subject	Posture	**Cinnarizine**	**Placebo**
LJ	HDT	20.2	25.7
	Seated	13.9	7.3
SE	HDT	18.0	24.2
	Seated	15.8	15.4
TJ	HDT	32.0	42.1
	Seated	36.0	26.7
	Mean	**22.65**	**23.57**
	± SE	**9.13**	**11.74**

TABLE R.2 BARORECEPTOR SENSITIVITY INDEX DERIVED FROM VALSALVA'S MANOEUVRE AFTER INGESTION OF CINNARIZINE OR PLACEBO (N = 3). Each value is the mean BRSI for a subject after the ingestion of cinnarizine immediately before parabolic flight in France (cinnarizine) or without cinnarizine under controlled environmental conditions in a climatic chamber in London (placebo).

No Significant difference was found between the BRSI values recorded in France under the influence of cinnarizine and those recorded in London without the use of the drug. A significant relationship ($r = 0.76$) was found to exist between measures.

In conclusion, cinnarizine does not appear to affect baroreflex responses to Valsalva's manoeuvre under controlled climatic or field conditions and is therefore suitable for use as an anti-motion sickness prophylactic for parabolic flight when baroreceptor sensitivity by means of the Valsalva's manoeuvre is measured.

RAW DATA

Subjects Physical Characteristics

Test Subjects

	Weight, kg				Age, yr	Height, cm
	Trained	Follow up1	Follow up2	Detrained		
JM	75	75.1		75.3	24	179
PP	82.5	81.2	83.8	85	26	180
GF	84	81.3	82.5	84.5	26	185.5
SE	76	75.3	76.5	76.2	33	181
IT	58.4	60.3	63.4	62.4	25	170
RW	74.2	79	78.5	79.5	28	187
LJ	54	54	54.4	54.5	29	162
Mean	**72.01**	**72.31**	**73.18**	**73.91**	**27.3**	**177.8**
SD	**11.5**	**10.8**	**11.7**	**11.4**	**3.0**	**8.9**
TJ	92		94	93.3	32	184

Resting Heart Rate, bpm

	Trained	Detrained
JM	47.6	46
PP	37.5	43
GF	73	65
SE	61	74
IT	68	81
RW	54	54
LJ	61	62
Mean	**57.44**	**60.71**
SD	**12.15**	**14.04**

Arterial Pressure, mmHg

	Trained		Detrained	
	SBP	DBP	SBP	DBP
JM	120	80	118	80
PP	115	75	116	76
GF	118	75	122	75
SE	122	86	124	85
RW	115	75	125	90
IT	108	64	110	64
LJ	116	65	112	85
TJ	115	80	114	80
Mean	**116.1**	**75.0**	**117.6**	**79.4**
SD	**4.2**	**7.5**	**5.6**	**8.0**

Subject Characteristics

Subjects Physical Characteristics

Control Subjects

	Weight, kg		Age, yr	Height, cm
	Initial	Final		
CC	65.2	65.5	31	165
CO	69.8	69.5	30	164
HM	72.4	73	30	168
CP	59	57.8	27	163
PG	75.9	74.7	29	184
RW	83	82.1	21	184
NR	64	63.8	33	175
Mean	**69.90**	**69.49**	**28.7**	**171.9**
SD	**8.06**	**7.99**	**3.9**	**9.2**

Resting Heart Rate, bpm

Initial	Final
66	64
63	58
77	83
76	75
59	57
58	57
57	56
Mean	65.14	64.29
SD	8.36	10.64

Arterial Pressure, mmHg

	Initial		Final	
	Systolic	Diastolic	Systolic	Diastolic
CC	115	72	116	75
CO	122	82	118	84
HM	128	88	125	85
CP	118	76	116	76
PG	120	80	122	85
RW	138	90	132	90
NR	119	72	120	80
Mean	**122.9**	**80.0**	**121.3**	**82.1**
SD	**7.8**	**7.2**	**5.7**	**5.4**

Fitness Related Measures

TEST SUBJECTS

	VO2max - ml/kg/min				Tolerance to LBNP Cumulative Stress Index	
	Trained	Follow up1	Follow up2	Detrained	Trained	Detrained
JM	79.3	63.1		62.5	913	1633
PP	71	66.6	68.2	60.7	717	775
GF	67.7	56.8	56.2	48.5	940	933
SE	64	60	60.7	54.6	1095	1170
IT	53.6	51.7	49.6	47.9	554	665
RW	55.5	52.2	51.4	51	741	867
LJ	53.3	50.1	47.3	49.7	540	720
Mean	**63.49**	**57.21**	**55.57**	**53.56**	**785.7**	**966.1**
SD	**9.9**	**6.3**	**7.8**	**5.9**	**206.7**	**337.9**
TJ	51.7	42.6	48	38	788	700

	Blood Volume (l)				Tolerance to LBNP Time to Pre-syncope (s)	
	Trained	Follow up1	Follow up2	Detrained	Trained	Detrained
JM	6.53	6.16		5.42	990	1157
PP	7	6.77	6.69	6.49	1220	1280
GF	6.48	6.38	6	6.1	1155	1204
SE	5.62	5.48	5.57	5.3	1450	1500
IT	4.6	4.34	4.5	4.42	1315	1790
RW	5.45	4.85	5.01	4.92	1004	1110
LJ	4.2	4.38	3.95	4	1335	1330
Mean	**5.70**	**5.48**	**5.29**	**5.24**	**1209.9**	**1338.7**
SD	**1.0**	**1.0**	**1.0**	**0.9**	**172.3**	**236.9**
TJ	6.37	6.55		6.4	1215	1140

Fitness Related Measures

CONTROL SUBJECTS

	VO2max - ml/kg/min		Tolerance to LBNP Cumulative Stress Index	
	Initial	Final	Initial	Final
CC	41.5	38.4	620	817
CO	34.8	34	1013	996
HM	35.4	34.5	723	840
CP	53.8	55.7	676	510
PG	56.8	54.1	840	644
RW	50.2	46.3	460	485
NR	45.9	47	900	880
Mean	**45.49**	**44.29**	**747.43**	**738.9**
SD	**8.67**	**8.89**	**185.7**	**195.0**

	Blood Volume (l)		Tolerance to LBNP Time to Pre-syncope (s)	
	Initial	Final	Initial	Final
CC	4.85	5.05	1269	1092
CO	4.7	4.48	1390	1260
HM	5.25	5.43	1160	1270
CP	5.1	5.02	1119	1050
PG	5.9	6.26	1260	935
RW	6.8	6.22	910	1377
NR	4.37	4.4	1305	1240
Mean	**5.28**	**5.27**	**1201.9**	**1174.9**
SD	**0.82**	**0.75**	**156.9**	**153.5**

BLOOD VOLUME VARIABLES

HbCO = Carboxyhaemoglobin (%) Hb = Haemoglobin (ml/dl)

Test Group Trained

	HbCO			Hb
	Baseline	Test	Diff	
JM	0.56	5.8	5.24	15.7
PP	0.53	5.49	4.96	15.5
GF	2.1	7.24	5.14	16.2
SE	0.56	6.9	6.34	15.1
RW	0.54	6.41	5.87	15.1
IT	0.67	9.26	8.59	14.1
LJ	0.27	8.64	8.37	12.3
Mean	**0.75**	**7.11**	**6.36**	**14.9**
SD	**0.61**	**1.41**	**1.53**	**1.30**

Control Group Initial

	HbCO			Hb
	Baseline	Test	Diff	
CC	0.57	9.2	8.63	12
CO	0.56	9.84	9.28	12
HM	3.26	9.22	5.96	13.8
CP	0.14	8.91	8.77	12.1
PG	0.35	6.24	5.89	15.5
RW	0.62	5.76	5.14	15.4
NR	0.54	7.81	7.27	17
Mean	**0.86**	**8.14**	**7.28**	**14.0**
SD	**1.07**	**1.59**	**1.65**	**2.04**

Follow Up 1

	HbCO			Hb
	Baseline	Test	Diff	
JM	nil	nil	nil	nil
PP	0.27	5.19	4.92	16.2
GF	2.38	7.54	5.16	16.4
SE	0.8	6.74	5.94	16.3
RW	0.55	7.33	6.78	16.4
IT	0.4	7.46	7.06	13.7
LJ	0.28	7.17	6.89	14.3
Mean	**0.78**	**6.91**	**6.13**	**15.6**
SD	**0.81**	**0.89**	**0.93**	**1.22**

Follow Up 2

	HbCO			Hb
	Baseline	Test	Diff	
JM	0.55	5.79	5.24	16.7
PP	0.27	5.18	4.91	16.4
GF	1.59	7.14	5.55	16.2
SE	0.81	4.84	4.03	16.3
RW	1.1	7.51	6.41	16.8
IT	0.41	7.33	6.92	13.9
LJ	0.66	8.88	8.22	13.3
Mean	**0.77**	**6.67**	**5.90**	**15.7**
SD	**0.45**	**1.45**	**1.40**	**1.43**

Test Group Detrained

	HbCO			Hb
	Baseline	Test	Diff	
JM	0.85	6.28	5.43	18.3
PP	0.85	4.6	3.75	17
GF	1.6	7.06	5.46	16.2
SE	0.7	7.2	6.5	15.8
RW	0.88	7.74	6.86	16
IT	0.28	7.23	6.95	14
LJ	0.56	11.9	11.34	12
Mean	**0.82**	**7.43**	**6.61**	**15.6**
SD	**0.41**	**2.22**	**2.36**	**2.05**

Control Group Final

	HbCO			Hb
	Baseline	Test	Diff	
CC	0.54	5.94	5.4	13.2
CO	1.9	9.26	7.36	13.1
HM	1.08	7.15	6.07	13.1
CP	0.54	9.35	8.81	12.2
PG	0.81	6.67	5.86	14.7
RW	0.39	5.86	5.47	15.9
NR	0.53	8.09	7.56	16.3
Mean	**0.83**	**7.47**	**6.65**	**14.1**
SD	**0.53**	**1.46**	**1.29**	**1.57**

Cardiovascular Responses to Progressive LBNP

Test Group Trained

	Systolic Arterial Pressure			Diastolic Arterial Pressure		
	Baseline	LBNP	Pre-Syncope	Baseline	LBNP	Pre-Syncope
JM	155	123	75	94	104	63
PP	94	85	52	53	56	19
GF	120	111	70	70	76	43
SE	123	113	87	83	82	53
RW	145	140	103	90	100	72
IT	123	124	83	78	82	53
LJ	120	113	103	80	78	67
Mean	**125.7**	**115.6**	**81.9**	**78.3**	**82.6**	**52.9**
SD	**19.6**	**16.8**	**18.3**	**13.6**	**16.0**	**17.9**

	Mean Arterial Pressure			Pulse Pressure		
	Baseline	LBNP	Pre-Syncope	Baseline	LBNP	Pre-Syncope
JM	114	110	67	61	21	12
PP	67	66	30	41	29	24
GF	87	88	52	50	35	27
SE	96	92	64	40	34	34
RW	108	113	82	55	44	31
IT	93	89	63	45	36	30
LJ	93	87	79	40	35	35
Mean	**94.0**	**92.1**	**62.4**	**47.4**	**33.4**	**27.6**
SD	**15.2**	**15.8**	**17.5**	**8.2**	**7.0**	**7.8**

All pressures in mmHg

	Heart Rate (bpm)		
	Baseline	LBNP	Pre-Syncope
JM	55	108	120
PP	44	76	24
GF	56	84	75
SE	66	94	102
RW	70	95	77
IT	56	70	54
LJ	55	99	114
Mean	**57.43**	**89.43**	**80.86**
SD	**8.44**	**13.39**	**34.35**

Cardiovascular Responses to Progressive LBNP

Control Group Initial

	Systolic Arterial Pressure			Diastolic Arterial Pressure		
	Baseline	LBNP	Pre-Syncope	Baseline	LBNP	Pre-Syncope
CC	142	136	85	80	83	53
CO	131	126	85	72	80	44
HM	125	118	80	77	77	45
CP	128	142	96	72	84	66
PG	120	122	95	77	89	74
RW	141	135	80	87	92	55
NR	126	114	100	85	91	80
Mean	**130.4**	**127.6**	**88.7**	**78.6**	**85.1**	**59.6**
SD	**8.3**	**10.4**	**8.2**	**5.9**	**5.7**	**14.1**

	Mean Arterial Pressure			Pulse Pressure		
	Baseline	LBNP	Pre-Syncope	Baseline	LBNP	Pre-Syncope
CC	101	101	64	62	53	32
CO	92	95	58	59	46	41
HM	93	91	57	48	41	35
CP	91	103	76	56	58	30
PG	91	100	81	43	33	21
RW	105	106	63	54	43	25
NR	99	99	87	41	23	20
Mean	**95.9**	**99.3**	**69.3**	**51.9**	**42.4**	**29.1**
SD	**5.6**	**5.1**	**12.0**	**8.0**	**11.8**	**7.6**

All pressures in mmHg

	Heart Rate (bpm)		
	Baseline	LBNP	Pre-Syncope
CC	70	120	96
CO	60	106	101
HM	60	85	66
CP	65	180	180
PG	53	89	74
RW	62	90	72
NR	58	87	96
Mean	**61.1**	**108.1**	**97.9**
SD	**5.4**	**34.1**	**38.8**

Progressive LBNP

Cardiovascular Responses to Progressive LBNP

Test Group Detrained

	Systolic Arterial Pressure			Diastolic Arterial Pressure		
	Baseline	LBNP	Pre-Syncope	Baseline	LBNP	Pre-Syncope
JM	135	116	68	74	74	53
PP	122	121	86	77	87	68
GF	124	130	71	75	77	48
SE	151	139	112	83	94	78
RW	123	121	85	88	87	71
IT	141	137	93	85	87	53
LJ	130	125	88	90	89	60
Mean	**132.3**	**127.0**	**86.1**	**81.7**	**85.0**	**61.6**
SD	**10.8**	**8.7**	**14.6**	**6.4**	**7.0**	**11.1**

	Mean Arterial Pressure			Pulse Pressure		
	Baseline	LBNP	Pre-Syncope	Baseline	LBNP	Pre-Syncope
JM	94	88	58	61	42	15
PP	92	98	74	45	34	28
GF	91	87	56	49	53	12
SE	106	109	89	68	45	34
RW	100	100	76	35	33	12
IT	104	104	66	56	56	40
LJ	103	100	69	40	37	28
Mean	**98.6**	**98.0**	**69.7**	**50.6**	**42.9**	**24.1**
SD	**6.2**	**8.0**	**11.3**	**11.8**	**9.0**	**11.2**

All pressures in mmHg

	Heart Rate (bpm)		
	Baseline	LBNP	Pre-Syncope
JM	45	115	150
PP	45	80	72
GF	64	77	71
SE	62	89	86
RW	69	107	102
IT	58	99	60
LJ	60	108	66
Mean	**57.6**	**96.4**	**86.7**
SD	**9.3**	**14.7**	**31.2**

Cardiovascular Responses to Progressive LBNP

Control Group Final

	Systolic Arterial Pressure			Diastolic Arterial Pressure		
	Baseline	LBNP	Pre-Syncope	Baseline	LBNP	Pre-Syncope
CC	147	160	102	85	88	76
CO	130	120	78	78	76	45
HM	122	146	110	80	95	65
CP	130	125	98	78	86	74
PG	121	120	120	70	79	70
RW	130	126	82	93	85	57
NR	121	130	100	82	92	75
Mean	**128.7**	**132.4**	**98.6**	**80.9**	**85.9**	**66.0**
SD	**9.2**	**15.0**	**14.7**	**7.1**	**6.7**	**11.4**

	Mean Arterial Pressure			Pulse Pressure		
	Baseline	LBNP	Pre-Syncope	Baseline	LBNP	Pre-Syncope
CC	106	112	85	62	72	26
CO	95	91	56	52	44	33
HM	94	112	80	42	51	45
CP	95	99	82	52	39	24
PG	87	93	87	51	41	50
RW	105	99	65	37	41	25
NR	95	105	83	39	38	25
Mean	**96.8**	**101.4**	**76.9**	**47.9**	**46.6**	**32.6**
SD	**6.6**	**8.6**	**11.6**	**8.9**	**12.0**	**10.7**

All pressures in mmHg

	Heart Rate (bpm)		
	Baseline	LBNP	Pre-Syncope
CC	70	140	83
CO	57	84	80
HM	78	111	75
CP	85	163	159
PG	60	114	102
RW	66	95	95
NR	58	100	80
Mean	**67.7**	**115.3**	**96.3**
SD	**10.7**	**27.5**	**31.4**

Progressive LBNP

Test Group Cardiopulmonary Baroreflex Detail

Trained					SUBJECT				Mean	SE
CVP	LBNP	JM	PP	GF	SE	RW	IT	LJ		
	0	9	10.4	10.2	9.8	6.2	7.6	8.5	8.81	1.52
	-5	7.8	9.1	9.5	8.1	4.9	4.9	6.4	7.24	1.88
	-10	7.2	8.5	7.9	7	3.7	3.1	4.8	6.03	2.14
	-15	5.7	5.5	6.1	5.7	2.9	2.8	3.6	4.61	1.45
	-20	5.1	5.2	7	5.1	2.7	0.6	2.6	4.04	2.16
	0	9.1	9	9.9	9.7	7.2	6.9	8.3	8.59	1.17
FBF										
	0	1.74	2.62	1.75	6.19	4.37	1.36	2.78	2.97	1.74
	-5	1.62	2.18	1.4	4.86	3.75	1.26	1.5	2.37	1.39
	-10	1.39	2.37	1.21	3.35	2.2	1.03	1.75	1.90	0.81
	-15	1.18	2.11	1.2	2.71	2.66	0.86	1.76	1.78	0.74
	-20	0.97	2.1	1.26	3.2	1.62	0.76	1.31	1.60	0.83
	0	1.67	2.29	1.66	2.74	2.88	0.11	3.25	2.09	1.06
FVR										
	0	59.8	33	48	15.3	20.1	58.8	29.9	37.84	17.95
	-5	64.2	39.9	66.7	19.5	23.5	63.5	55.3	47.51	19.93
	-10	74.8	36.7	69.4	28.4	40	77.7	47.4	53.49	20.10
	-15	88.1	41	70	35	33.1	93	47.2	58.20	25.26
	-20	107.2	41.4	60	29.7	54.3	105.3	63.4	65.90	29.85
	0	62	38	50.6	31	30.6	72.1	25.5	44.26	17.72

Detrained					SUBJECT				Mean	SE
CVP	LBNP	JM	PP	GF	SE	RW	IT	LJ		
	0	8.4	8.8	12	8.6	6.2	8.1	8.6	8.67	1.71
	-5	9.8	7.5	10.5	7.1	4.7	6.4	7.3	7.61	1.98
	-10	8.4	6.8	9.2	5.5	4	6.1	4.7	6.39	1.90
	-15	9.4	6	7.9	4.1	3.3	3.3	5.5	5.64	2.34
	-20	7	4.8	6.4	3.1	2.2	2.2	3.9	4.23	1.93
	0	10.1	7.9	12.7	8.7	5.3	6.8	8.1	8.51	2.38
FBF										
	0	0.813	2.55	2.14	2.86	4.88	1.67	2.37	2.47	1.26
	-5	1.03	2.34	1.22	2.52	3.44	1.59	1.99	2.02	0.83
	-10	0.7	2.14	1.19	2.36	2.8	1.53	2.18	1.84	0.73
	-15	0.83	1.64	0.93	2.3	2.48	1.43	1.88	1.64	0.63
	-20	0.61	1.45	1.22	1.99	2.5	0.95	1.15	1.41	0.64
	0	1.15	2.44	1.89	2.41	3.71	1.66	2.31	2.22	0.80
FVR										
	0	110.7	38.6	41.6	34.7	19.1	48.5	33.9	46.73	29.61
	-5	87.5	42.9	73	39.4	27	50.9	40.4	51.59	21.22
	-10	128.6	43.9	74.8	42	33.2	52.9	36.9	58.90	33.67
	-15	108.4	50.3	95.7	43.1	37.5	56.6	42.8	62.06	28.23
	-20	147.5	52.9	73	49.8	37.2	85.3	69.9	73.66	36.36
	0	78.3	36.8	47.1	41	25.1	48	35.2	44.50	16.81

CVP Central Venous Presssure (mmHg)
FBF Forearm Blood Flow ($ml.dl^{-1}$)
FVR Forearm Vascular Resistance ($u\ mmHg^{-1}$)

Cardiopulmonary BRF Detail

Control Group Cardiopulmonary Baroreflex Detail

Initial					SUBJECT				Mean	SE
CVP	LBNP	CC	CO	HM	CP	PG	RW	NR		
	0	10.3	4.9	11.6	7.9	6.7	6.0	7.93	7.90	2.36
	-5	8.3	3.6	10.6	7.4	4.8	5.2	7.63	6.79	2.40
	-10	7.7	2.2	8.9	5.6		4.0	6.18	5.76	2.44
	-15	6.3	1.7	7.7	4.5	2.0	2.8	3.93	4.13	2.23
	-20	5.2	1.1	5.5	1.8	1.2	1.6	3.43	2.83	1.89
	0	9.2	5.6	11.5	7.7			6.83	8.17	2.28
FBF										
	0	2.5	2.5	2.1	2.2	1.4	1.9	2.10	2.11	0.39
	-5	2.1	2.5	1.6	2.2	1.2	1.9	2.00	1.93	0.42
	-10	1.8	2.2	1.6	1.7		1.8	1.27	1.72	0.29
	-15	1.1	2.0	1.5	1.4	0.9	1.2.	1.14	1.31	0.37
	-20	1.2	1.7	1.1	1.4	0.7	1.0	0.64	1.11	0.38
	0	2.3	2.2	1.7	2.9			1.84	2.19	0.47
FVR										
	0	31.8	37.1	44.2	38.9	52.8	55.7	42.70	43.31	8.52
	-5	37.2	38.5	56.2	38.6	61.7	57.2	44.80	47.74	10.36
	-10	45.5	43.5	55.8	49.7		60.1	70.10	54.12	10.01
	-15	74.4	47.2	62.3	60.4	85.1	89.2	78.60	71.03	15.02
	-20	64.2	54.8	85.8	62.2	105.7	102.9	140.00	87.94	30.49
	0	34.8	42.3	53.2	29.8			48.70	41.76	9.63

Final					SUBJECT				Mean	SE
CVP	LBNP	CC	CO	HM	CP	PG	RW	NR		
	0	10	8.6	9.4	4.5	5.2	5.9	6.3	7.13	2.18
	-5	8.7	7.3	9	3.3	4.5	4.4	5.1	6.04	2.27
	-10	7.5	5.5	6.5	3.1	3.1	3.7	4.2	4.80	1.73
	-15	6.2	4.4	5.9	0.3	2.6	2.7	2.8	3.56	2.08
	-20	4.8	3.6	5.6	0	2.4	1.4	1.7	2.79	1.99
	0	9.1	8.8	10.4	4.3	5.7	4.9	4.9	6.87	2.48
FBF										
	0	2.74	2.64	3.2	2.21	3.05	2	2.66	2.64	0.43
	-5	2.23	2.38	2.77	0.92	1.73	1.96	1.69	1.95	0.59
	-10	1.89	1.39	2.62	1.1	1.64	1.13	1.76	1.65	0.52
	-15	2.01	1.43	2.02	0.96	1.49	1.03	1.69	1.52	0.42
	-20	1.31	1.28	2.02	0.86	0.69	0.99	1.51	1.24	0.45
	0	2.53	2.35	2.62	1.32	3.5	1.25	1.57	2.16	0.82
FVR										
	0	26.3	30.3	27.8	40.3	26.7	47.5	35.1	33.43	8.02
	-5	32.3	34	32.13	96.8	46.2	48.5	55	49.28	22.79
	-10	38.1	58.3	34	81	43.8	84.1	52.8	56.01	19.93
	-15	35.8	56.65	44.06	92.8	53.7	92	55	61.43	22.37
	-20	55	63.3	44.06	103.6	115.9	96	61.6	77.07	27.62
	0	28.5	34.4	33.97	67.5	22.9	76	59.2	46.07	21.04

CVP Central Venous Presssure (mmHg)
FBF Forearm Blood Flow ($ml.dl^{-1}$)
FVR Forearm Vascular Resistance ($\mu mmHg^{-1}$)

Cardiopulmonary Baroreflex Slopes

TEST GROUP

	Cardiopulmonary Baroreflex Gain		
	Trained	**Detrained**	
JM	-12.8	-8.19	U/mmHg
PP	-1.44	-3.75	
GF	-4.74	-6.16	
SE	-3.85	-2.38	
IT	-6.98	-5.16	
RW	-7.82	-4.94	
LJ	-4.99	-3.7	
Mean	**-6.09**	**-4.90**	
SD	**3.6**	**1.9**	
TJ	3.53	1.22	

CONTROL GROUP

	Initial	**Final**	
CC	-6.55	-5.6	U/mmHg
CO	-4.3	-7.1	
HM	-6.01	-3.7	
CP	-4.35	-11.35	
PG	-9.14	-8.11	
RW	-11.48	-12.5	
NR	-16.74	-5.58	
Mean	**-8.37**	**-7.80**	
SD	**4.51**	**3.23**	

Cardiopulmonary BR Detail

Carotid Baroreflex Responses

Test Group

Mean Change in R-R Interval (s)

	Trained				Detrained			
Neck Press:	**-17**	**-30**	**-44**	**-58**	**-17**	**-30**	**-44**	**-58**
JM	0.242	0.41	0.468	0.56	0.17	0.257	0.28	0.391
PP	0.14	0.21	0.43	0.482	0.17	0.195	0.214	0.288
GF	0.093	0.102	0.123	0.163	0.047	0.078	0.111	0.126
SE	0.077	0.126	0.17	0.19	0.097	0.107	0.125	0.118
RW	0.28	0.374	0.43	0.466	0.12	0.205	0.208	0.214
IT	0.368	0.476	0.574	0.554	0.06	0.086	0.125	0.117
LJ	0.254	0.331	0.36	0.4	0.119	0.193	0.242	0.185
Mean	**0.208**	**0.290**	**0.365**	**0.402**	**0.112**	**0.160**	**0.186**	**0.206**
SE	**0.107**	**0.145**	**0.163**	**0.164**	**0.048**	**0.069**	**0.066**	**0.103**

Control Group

Mean Change in R-R Interval (s)

	Initial				Final			
Neck Press:	**-18**	**-29**	**-45**	**-59**	**-18**	**-29**	**-45**	**-59**
CC	0.223	0.401	0.386	0.511	0.228	0.4	0.41	0.41
CP	0.109	0.168	0.172	0.332	0.077	0.15	0.267	0.224
HM	0.091	0.154	0.168	0.274	0.073	0.105	0.201	0.208
PG	0.09	0.132	0.16	0.159	0.068	0.083	0.156	0.185
Oz	0.08	0.11	0.14	0.158	0.056	0.073	0.112	0.169
NR	0.036	0.083	0.079	0.157	0.04	0.033	0.078	0.158
RW	0.035	0.046	0.052	0.052	0.028	0.012	0.038	0.05
Mean	**0.095**	**0.156**	**0.165**	**0.235**	**0.081**	**0.122**	**0.180**	**0.201**
SE	**0.063**	**0.116**	**0.108**	**0.152**	**0.067**	**0.131**	**0.127**	**0.108**

Carotid Baroreflex Gain

Test Group

	Trained	Detrained	
JM	7.3	3.8	ms/mmHg
PP	11.1	1.4	
GF	1.2	2.3	
SE	3.4	1	
IT	7.6	2.4	
RW	4	2.8	
LJ	3.5	3.5	
Mean	**5.44**	**2.46**	
SD	**3.4**	**1.0**	
TJ	13.6	5.4	

Control Group

	Initial	Final	
CC	1.1	1.3	ms/mmHg
CO	4.5	2.8	
HM	5.9	6.2	
CP	0.6	0.4	
PG	0.3	1.4	
RW	2.6	3.5	
NR	2.8	6.4	
Mean	**2.54**	**3.14**	
SD	**2.08**	**2.39**	

Carotid BR Detail

Parabolic Flight Microgravity BRSI Reproducibility & Baseline Measures

BRSI Reproducibility - Subject SE

	Campaign 1			Campaign 2	
Flight 1	1	2	3	1	2
	11.6	14.2	13.5	8.67	9.4
	12.96	14.5	12.8	10.5	9.9
	8.3	12.1	16.6	19.41	16.2
	14.5	17.44		13.8	11.5
	8.7			11.56	11.8
	11.6				11.3
	11.1				
Mean	**11.25**	**14.56**	**14.29**	**12.79**	**11.76**
SE	**2.2**	**2.2**	**2**	**4.14**	**2.41**

Grand Mean
12.9

Baseline Measures - All Subjects

Arterial Pressure (mmHg)

	HDT	1.8G	1G
Day 1	120	105	102
	118	90	90
	110	98	90
Mean	**116.0**	**97.7**	**94.0**
SD	**5.3**	**7.5**	**6.9**
Day 2	124	130	130
	121	118	108
	111	108	110
Mean	**118.7**	**118.7**	**116.0**
SD	**6.8**	**11.0**	**12.2**
Day 3	115	113	113
	113	100	100
	111	100	90
Mean	**113.0**	**104.3**	**101.0**
SD	**2.0**	**7.5**	**11.5**
Grand Mean	**115.9**	**106.9**	**103.7**
SE	**5.06**	**12.04**	**13.30**

Heart Rate (bpm)

	HDT	1.8G	1G
Day 1	63	66	81
	72	69	90
	81	78	87
Mean	**72.0**	**71.0**	**86.0**
SD	**9.0**	**6.2**	**4.6**
Day 2	75	66	75
	66	69	81
	66	68	84
Mean	**69.0**	**67.7**	**80.0**
SD	**5.2**	**1.5**	**4.6**
Day 3	78	69	70
	75	66	72
	70	72	78
Mean	**74.3**	**69.0**	**73.3**
SD	**4.0**	**3.0**	**4.2**
Grand Mean	**71.8**	**69.2**	**79.8**
SE	**6.04**	**3.83**	**6.70**

First Campaign Heart Rate and Blood Pressure According to Valsalva Phase

Head-down Tilt

Pre-Flight

	Pre-HR	Pre MAP	Ph2 Min PP	Ph2 Min HR	Ph 4 max SBP	2-4 max SBP diff
RW	85.7	111.7	38.07.	108	140.10	47.80
IT	65	99.7	43.8	68	137.30	37.00
SS	65	111	70.2	78	136.3	65.80
JM	71.6	114.7	36.95	98	148.4	43.70
LJ	87.8	120.7	38.83	114	162.90	31.10
GF	73.4	104	54.53	84	138	65.50
SE1	80	131.7	44.8	89	173.7	15.10
SE2	80	132.7	51.57	92	169.00	17.40
SE3	70.6	131.7	41.65	98	141.80	14.40
Mean	**75.5**	**117.5**	**46.7**	**92.1**	**149.7**	**37.5**
SE	**8.4**	**10.6**	**10.6**	**14.4**	**14.8**	**20.0**

Microgravity

	Pre-HR	Pre MAP	Ph2 Min PP	Ph2 Min HR	Ph 4 max SBP	2-4 max SBP diff
RW	97	129	41.1	130.2	203.50	75.5
IT	66	102	39	82.0	120.9	72.69
SS	72.3	133.4	44.4	85.4	176.33	63.9
JM	66.2	107.9	31.4	106.0	163.60	35.4
LJ	92	95.3	30.7	125.9	143.70	103.6
GF	85.7	117	37.4	105.0	178.03	33.2
SE1	83.2	129.2	44.9	107.7	181.43	53.6
SE2	70.6	121.6	46.9	106.5	175.20	55.2
SE3	82	113.7	48.5	110.3	158.10	60.2
Mean	**79.4**	**116.6**	**40.5**	**106.6**	**166.8**	**61.5**
SE	**11.2**	**13.1**	**6.4**	**15.8**	**23.9**	**21.5**

Post-Flight

	Pre-HR	Pre MAP	Ph2 Min PP	Ph2 Min HR	Ph 4 max SBP	2-4 max SBP diff
RW	77.4	113.3	33.7	111	148.57	27.80
IT		74.5		66	106.8	11.60
SS						
JM	49.3	128.7	46.8	70	167.25	31.05
LJ	72	83.3	33.3	101	117.20	30.09
GF						
SE1	80	109.3	43.57	94.9	150.83	31.43
SE2		115.0		90	134.90	6.10
SE3		109.8				
Mean	**69.7**	**104.8**	**39.3**	**88.8**	**137.6**	**23.0**
SE	**14.0**	**19.0**	**6.9**	**17.6**	**22.6**	**11.2**

Pre-HR	Baseline Heart rate
Pre MAP	Baseline Mean Arterial Pressure
Ph2 Min PP	Minimum Pulse Pressure during phase 2 of Valsalva's manoeuvre
Ph2 Min HR	Minimum heart rate during phase 2 of Valsalva's manoeuvre
Ph 4 max SBP	Maximum systolic arterial pressure during phase 4 of Valsalva's manoeuvre
2-4 max SBP diff	Difference betqeen systolic pressure of phase 2 and phase 4 of Valsalva's manoeuvre

First Campaign Heart Rate and Blood Pressure According to Valsalva Phase

Seated

Pre-Flight

	Pre-HR	Pre MAP	Ph2 Min PP	Ph2 Min HR	Ph 4 max SBP	4 max SBP diff
RW	92	124	46.5	120.0	144.4	31.2
IT	75	92.3	49.43	75.0	112.5	17.9
SS	66	116.7	62.38	75.0	147.90	34.0
JM	82.2	127.2	44.17	103.0	173.9	67.7
LJ	102.9	113	35.6	120.0	151.9	44.7
GF	77.4	112	45.1	93.0	148.5	27.4
SE1	85.7	130.3	46	85.0	171.20	47.0
SE2	85.7	127.7	50.07	93.1	168.2	40.1
SE3	76.6	129.1	42.7	101.0	144.30	27.9
Mean	**82.61**	**119.1**	**46.9**	**96.1**	**151.4**	**37.5**
SE	**10.7**	**12.3**	**7.2**	**16.8**	**23.8**	**23.9**

Microgravity

	Pre-HR	Pre MAP	Ph2 Min PP	Ph2 Min HR	Ph 4 max SBP	4 max SBP diff
RW	97	115.3	40.1	130.2	175.20	75.5
IT	66	86.8	38	82.0	122.9	72.69
SS	72.3	118.2	43.4	85.4	176.33	63.9
JM	66.2	92.7	30.4	106.0	163.60	35.4
LJ	92	80.1	29.7	125.9	143.70	103.6
GF	85.7	102.5	36.4	105.0	178.03	33.2
SE1	83.2	114.0	43.9	107.7	181.43	53.6
SE2	70.6	110.8	45.1	106.5	201.90	55.2
SE3	82	103.5	47.5	110.3	158.10	60.2
Mean	**79.4**	**102.7**	**39.4**	**106.6**	**166.8**	**61.5**
SE	**11.2**	**13.5**	**6.3**	**15.8**	**23.1**	**21.5**

Post-Flight

	Pre-HR	Pre MAP	Ph2 Min PP	Ph2 Min HR	Ph 4 max SBP	4 max SBP diff
RW	96	89.7	27.25	118	153.60	60.20
IT		74.9		76	106.7	16.60
SS						
JM	58.1	127.7	28.87	90	166.2	52.00
LJ	88.9	80.7	21.5	123	110.9	
GF						
SE1	87.8	117.8	41.2	101	155.4	68.20
SE2		116.9		96.9	157.5	41.20
SE3	92	118.3				
Mean	**84.56**	**103.7**	**29.7**	**100.8**	**141.7**	**47.6**
SE	**15.1**	**21.3**	**8.3**	**17.5**	**25.9**	**22.7**

Pre-HR	Baseline Heart rate
Pre MAP	Baseline Mean Arterial Pressure
Ph2 Min PP	Minimum Pulse Pressure during phase 2 of Valsalva's manoeuvre
Ph2 Min HR	Minimum heart rate during phase 2 of Valsalva's manoeuvre
Ph 4 max SBP	Maximum systolic arterial pressure during phase 4 of Valsalva's manoeuvre
2-4 max SBP diff	Difference betqeen systolic pressure of phase 2 and phase 4 of Valsalva's manoeuvre

Second Campaign Heart Rate and Blood Pressure According to Valsalva Phase

Head-down Tilt

Pre-Flight

	Pre-HR	Pre MAP	Ph2 Min PP	Ph2 Min HR	Ph 4 max SBP	2-4 max SBP diff
LJ	66	76	33	88	107.5	24.5
CD	77	110.3	55	95	180	44.3
GF	65.5	93.6	45.5	81.7	156.5	32.5
IT	63.5	88	63	66.5	116.5	0
JM	72	93	67.7	82.3	153.3	13.3
PP	63	84.7	47.7	81	145	21.3
RW	77.3	94.3	35.8	105.3	156.5	46.5
SE	71.3	99	46.7	89.3	167.7	38.7
Mean	**69.5**	**92.4**	**49.3**	**86.1**	**147.9**	**27.6**
SE	**5.8**	**10.6**	**12.1**	**11.4**	**24.6**	**16.0**

Microgravity

	Pre-HR	Pre MAP	Ph2 Min PP	Ph2 Min HR	Ph 4 max SBP	2-4 max SBP diff
LJ	72	85.9	34.7	99.9	134.6	25.9
CD	99	85.5	49	136	216.5	90.7
GF	68.4	87.8	46.9	77.9	150.8	50.9
IT	55.5	89	29	69.5	113.8	11
JM	56.2	86.5	25.5	93.8	146.3	55.3
PP	69.9	85.7	52	83	160.3	48.6
RW	92.7	89.9	29.9	122.1	174.9	84.9
SE	78.2	87.4	25.8	95.8	155.6	89.4
Mean	**74.0**	**87.2**	**36.6**	**97.3**	**156.6**	**57.1**
SE	**15.6**	**1.6**	**11.0**	**22.3**	**30.2**	**29.7**

Post-Flight

	Pre-HR	Pre MAP	Ph2 Min PP	Ph2 Min HR	Ph 4 max SBP	2-4 max SBP diff
LJ	66.3	82	28	88.3	108	9.3
CD	59	90.7	50.3	71.3	135.7	10.5
GF	60	77.7	42.7	71.3	122.7	3.3
IT	65	77	30.3	69.7	110.3	18
JM	56.7	94	39.7	64.3	121	7.7
PP	49.7	76.3	39.7	61.3	121.3	14
RW	90.7	72.9	40.3	107	135.7	40.7
SE	71.3	73	21.3	90.3	127	66.7
Mean	**64.8**	**80.5**	**36.5**	**77.9**	**122.7**	**21.3**
SE	**12.3**	**7.9**	**9.3**	**15.7**	**10.2**	**21.6**

Pre-HR	Baseline Heart rate
Pre MAP	Baseline Mean Arterial Pressure
Ph2 Min PP	Minimum Pulse Pressure during phase 2 of Valsalva's manoeuvre
Ph2 Min HR	Minimum heart rate during phase 2 of Valsalva's manoeuvre
Ph 4 max SBP	Maximum systolic arterial pressure during phase 4 of Valsalva's manoeuvre
2-4 max SBP diff	Difference betqeen systolic pressure of phase 2 and phase 4 of Valsalva's manoeuvre

Second Campaign Heart Rate and Blood Pressure According to Valsalva Phase

Seated

Pre-Flight

	Pre-HR	Pre MAP	Ph2 Min PP	Ph2 Min HR	Ph 4 max SBP	2-4 max SBP diff
LJ	78	85	30.5	130	124.5	30.5
CD	68.3	87.3	49.7	100.7	140	61.3
GF	77.2	84.5	49.7	91.5	153.8	25.2
IT	65.7	81.3	24	70.7	97.7	0
JM	65.5	97.5	32.3	87.8	162.5	50.5
PP	53.7	86.7	54.7	76.3	151	34.7
RW	78.7	100.7	31.7	113.3	171.7	64
SE	71.3	92.3	37.3	88.3	147.7	44.7
Mean	**69.80**	**89.4**	**38.7**	**94.8**	**143.6**	**38.9**
SE	**8.5**	**6.8**	**11.2**	**19.4**	**23.8**	**23.9**

Microgravity

	Pre-HR	Pre MAP	Ph2 Min PP	Ph2 Min HR	Ph 4 max SBP	-4 max SBP diff
LJ	72	85.9	34.7	99.9	134.6	25.9
CD	99	85.5	49	136	216.5	90.7
GF	68.4	87.8	46.9	77.9	150.8	50.9
IT	55.5	89	29	69.5	113.8	-11
JM	56.2	86.5	25.5	93.8	146.3	55.3
PP	69.9	85.7	52	83	160.3	48.6
RW	92.7	89.9	29.9	122.1	174.9	84.9
SE	78.2	87.4	25.8	95.8	155.6	89.4
Mean	**74.0**	**87.2**	**36.6**	**97.3**	**156.6**	**57.1**
SE	**15.6**	**1.6**	**11.0**	**22.3**	**30.2**	**29.7**

Post-Flight

	Pre-HR	Pre MAP	Ph2 Min PP	Ph2 Min HR	Ph 4 max SBP	-4 max SBP diff
LJ	71	90.3	29.7	102	142	29.3
CD	72.4	76.3	42.4	92	146.2	49.3
GF	66.3	83	38.5	80	129.5	11.5
IT	64.7	76.3	29.7	77.7	114	22.3
JM	46.3	86.3	45.7	50.3	125.7	0
PP	52	84.3	32.3	59.3	125.3	13.4
RW	95.3	77.7	41.3	120	150.6	47.3
SE	72	71.3	24.7	84	139	72.7
Mean	**67.50**	**80.7**	**35.5**	**83.2**	**134.0**	**30.7**
SE	**14.8**	**6.3**	**7.4**	**22.3**	**12.4**	**22.7**

Pre-HR	Baseline Heart rate
Pre MAP	Baseline Mean Arterial Pressure
Ph2 Min PP	Minimum Pulse Pressure during phase 2 of Valsalva's manoeuvre
Ph2 Min HR	Minimum heart rate during phase 2 of Valsalva's manoeuvre
Ph 4 max SBP	Maximum systolic arterial pressure during phase 4 of Valsalva's manoeuvre
2-4 max SBP diff	Difference betqeen systolic pressure of phase 2 and phase 4 of Valsalva's manoeuvre

Parabolic Campaign Baroreceptor Sensitivity Index Data

Campaign 1

	Pre		Microgravity	Post		Mean of Pre and Post Combined	
	HDT	Seated		HDT	Seated	HDT	Seated
SE1	13.83	9.95	11.23	18.17	13.19	16	11.6
GF	29.96	44.39	8.01	29.96	44.4	29.97	44.4
SS	40.57	40.9	36.37	40.57	40.9	40.56	40.9
IT	30.89	15.3	23.87	55.45	60.9	43.17	38.1
RW	21.08	22.44	14.00	26.8	23.36	23.94	22.9
JM1	33.28	22.1	18.31	24.32	18.92	28.8	20.5
LJ	29.39	21.86	4.28	29.77	25.14	29.58	23.5
Mean	**28.43**	**25.28**	**16.58**	**32.15**	**32.40**	**30.29**	**28.84**
SE	**8.64**	**12.74**	**10.86**	**12.31**	**16.90**	**9.30**	**12.28**
SE2	15.5	21.08	14.56	13.92	22.4		
SE3	17.9	14.29	14.29				
Mean	**16.7**	**17.7**	**14.4**	**13.9**	**22.4**		
SE	**1.7**	**4.8**	**0.2**				

Campaign 2

	Pre		Microgravity	Post		Mean of Pre and Post Combined	
	HDT	Seated		HDT	Seated	HDT	Seated
SE1	22.2	13.3	12.8	14.7	15.5	18.45	14.40
JM1	25.3	26.6	17.3	33.5	31.7	29.40	29.15
IT	29.64	34.27	24.1	19.3	23.3	24.47	28.79
CD	21.8	22.5	5.7	34.1	22.8	27.95	22.65
PP	56.01	79.3	40.13	33.08	23.65	44.55	51.48
GF	10.68	17.26	13.56	15.3	30.38	12.99	23.82
RW	13.7	18.2	12.7	17.3	15.2	15.50	16.70
LJ	10.51	14.43	3.58	30.1	13.55	20.31	13.99
TJ	36.9	18.6	17.2	34.1	45.3	35.50	31.95
Mean	**25.2**	**27.2**	**16.3**	**25.7**	**24.6**	**25.46**	**25.88**
SE	**14.5**	**20.6**	**10.8**	**8.8**	**10.1**	**10.1**	**11.6**
SE1	22.2	13.3	12.8	15.5	14.7		
SE3	17.2	18	11.7	18.7	13.6		
Mean	**19.7**	**15.7**	**12.3**	**17.1**	**14.2**		
SE	**3.5**	**3.3**	**0.8**	**2.3**	**0.8**		
JM1	25.3	26.6	17.3	33.5	31.7		
JM2				16.3	11.8		
JM3	17.6	17.1	17.5	21.5	21.7		
Mean	**21.5**	**21.9**	**17.4**	**23.8**	**21.7**		
SE	**5.4**	**6.7**	**0.1**	**8.8**	**10.0**		

BRSI = $ms.mmHg^{-1}$

Parabolic BRSIs

Baroreceptor Sensitivity Index According to Trained State

Detrained

	Pre Flight		Microgravity	Post Flight		Combined Pre&Post	
	HDT	Seated		HDT	Seated	HDT	Seated
SE1	13.83	9.95	11.23	18.17	13.19	16.00	11.57
JM1	25.3	26.6	17.3	31.7	33.5	28.50	30.05
IT	29.64	34.27	24.1	19.3	23.3	24.47	28.79
RW	21.08	22.44	14.00	26.8	23.36	23.94	22.90
LJ	29.39	21.86	4.28	29.77	25.14	29.58	23.50
GF	17.26	10.68	13.56	15.3	30.38	16.28	20.53
Mean	**22.75**	**20.97**	**14.08**	**23.51**	**24.81**	**23.13**	**22.89**
SE	**6.5**	**9.4**	**6.6**	**6.8**	**7.0**	**5.84**	**6.63**
CD	21.8	22.5	5.7	34.1	22.8		

Trained

	Pre Flight		Microgravity	Post Flight		Combined Pre&Post	
	HDT	Seated		HDT	Seated	HDT	Seated
SE1	22.2	13.3	12.8	15.5	14.7	18.85	14.00
JM1	33.28	22.1	18.31	24.32	18.92	28.80	20.51
IT	30.89	15.3	23.87	55.45	60.9	43.17	38.10
RW	13.7	18.2	12.7	15.2	17.3	14.45	17.75
LJ	10.51	14.43	3.58	30.1	13.55	20.31	13.99
GF	29.96	44.39	8.01	29.96	44.4	29.96	44.40
Mean	**23.4**	**21.3**	**13.2**	**28.4**	**28.3**	**25.92**	**24.79**
SE	**9.6**	**11.8**	**7.2**	**14.8**	**19.7**	**10.35**	**13.13**
PP	56.01	79.3	40.13	33.08	23.65		
SS	40.57	40.9	36.37				
TJ	36.9	18.6	17.2	34.1	45.3		

BRSI ms.mmHg^{-1}

BRSI vs Fitness

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Abstracts of the *69th Aerospace Medical Association conference*, Seattle.

AN EXAMINATION OF ARTERIAL BAROREFLEX FUNCTION IN ATHLETES DURING MICROGRAVITY AND SIMULATED MICROGRAVITY. S. Evetts. King's College London, Kensington Campus, Campden Hill Road, London W8 7AH, UK.

INTRODUCTION. Orthostatic intolerance similar to that experienced by astronauts returning from orbit has been reported in athletic subjects. The exact nature of the cause of both microgravity and fitness related orthostatic intolerance has yet to be determined. One potential mechanism is an alteration in baroreceptor function as a result of exposure to microgravity or due to exercise training. This study measured the closed loop arterial baroreceptor responses of athletic subjects whilst in seated and 6° head-down tilt (HDT) positions at 1G and whilst weightless in order to examine whether differences in baroreflex sensitivity existed between the conditions of normal gravity, simulated microgravity and acute exposure to real microgravity. METHOD. Seven healthy athletic subjects (mean VO_2max of 57.9 ± 8.4 ml.kg.$^{-1}$min^{-1}) had their baroreflex sensitivity index (BRSI) measured by recording R-R intervals and digital arterial pressure during Valsalva's Manoeuvres (VM) performed at an expiratory pressure of 40 mmHg for 10 seconds. The slope of the R-R interval/systolic pressure relationship obtained from phase IV of the VM provided the measure of baroreflex sensitivity. The VM were conducted in the seated and 6° HDT positions immediately before and after European Space Agency sponsored parabolic flights and whilst weightless during the flights. RESULTS. Group mean pre- to post-flight BRSI values were not significantly different for either seated ($p > 0.05$) or HDT ($p > 0.05$) positions. The mean microgravity BRSI (16.57 ± 10.8 ms.mmHg^{-1}) was found to be significantly less than ($p < 0.05$) that of seated (28.84 ± 12.27 ms.mmHg^{-1}) and HDT (30.29 ± 9.29 ms.mmHg^{-1}) values. CONCLUSION. Acute exposure to microgravity may reduce closed-loop baroreflex sensitivity in athletic subjects. The use of 6° HDT as a mode of microgravity simulation may not be appropriate when examining closed-loop baroreflex function at $+1G_z$.

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THE CARDIOVASCULAR EFFECTS OF 6 HOURS OF 6° HEAD-DOWN TILT UPON ATHLETES AND NON-ATHLETES. S.Evetts & T. Russomano. King's College London, Kensington Campus, Campden Hill Road, London, W8 7AH, U.K.

METHOD. The cardiovascular responses of athletes and non-athletes to a simulation of microgravity comprising a 6 hour exposure to 6° head-down tilt (HDT) were investigated. Eight healthy male subjects, aged 19 - 33, were placed in athletic (n = 4) and non-athletic (n = 4) groups according to their directly measured maximum oxygen uptake values. The effects of the 6 hour exposure to 6° HDT were studied by recording ECG and arterial blood pressure at intervals during HDT and during 10 minutes of 70° head-up tilt (HUT) before and after the HDT. Baroreceptor responsiveness was examined by recording the heart rate and blood pressure responses to Valsalva's manoeuvres (mouth pressure of 40 mmHg held for 15 seconds) performed before and after HDT, whilst the subject was horizontal and in the 70° HUT position. RESULTS. The increase of heart rate and the decreases of diastolic and systolic pressure produced by the HUT were significantly greater ($p < 0.05$) after the 6 hour exposure to 6° HDT than before. The athletic group were also found to have a significantly greater mean baroreflex slope when compared to that of the non-athletic group mean ($p < 0.05$). Of seven subjects who successfully completed the study none fainted during orthostatic stress before HDT, but two fainted after HDT. The subjects who entered syncope during HUT were both athletes. CONCLUSION. The results of this investigation support the hypothesis that physical fitness and microgravity simulation both adversely affect baroreflex sensitivity.